sound of the heart in time and in character. Whether it is due to the same unknown mechanism causing the normal third sound is not known. It seems to me likely that it is. It may be caused by the opening snap of the auriculoventricular valves under unusually great venous and intra-auricular pressure (from stasis) plus dilatation of the ventricular cavities; it may be the result of vibration of the dilated ventricular walls from the rapid stream of blood entering early in diastole; it may be due to other causes. The mesodiastolic gallop rhythm is apparently either the presystolic or the protodiastolic placed centrally in diastole by the fast

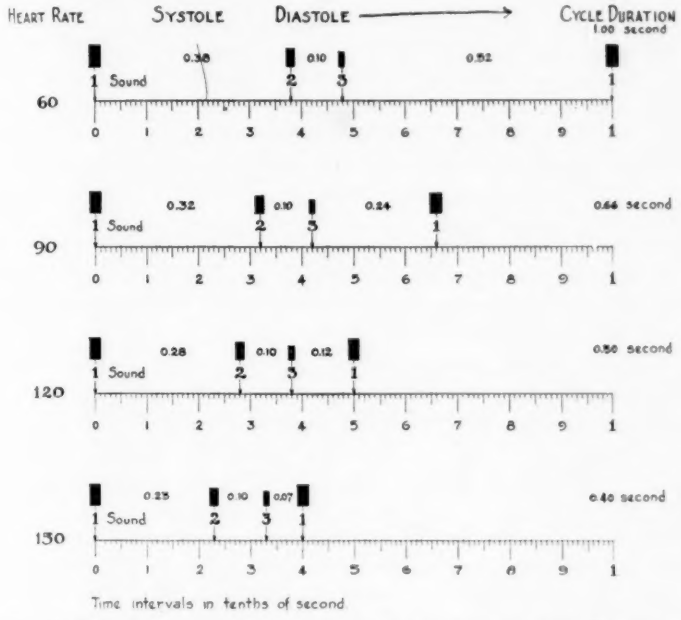

Fig. 2.—Protodiastolic gallop rhythm, showing the effect of changing heart rate on relative position of the three heart sounds.

heart rate; it is probable that there is not actually a mesodiastolic type. In these three timings of the diastolic gallop rhythm the interval of systole is, except in slow pulse rates, considerably longer than either division of diastole; the longest pause is systole. Finally, systolic gallop rhythm is rare and of unknown cause; it has been suggested by Bard and others that it is the result of a dissociation of the muscular and valvular elements of the first sound in cardiac weakness. It may, except by graphic records, be difficult to distinguish from the presystolic gallop rhythm, since it is protosystolic in time.

Gallop rhythm must not be confused with simple rapid reduplication of the heart sounds or with frustrate premature contractions occurring bigeminally, as it not infrequently is by medical men unacquainted with the differentiation, especially in respect to reduplication of the second heart sound.

Gallop rhythm is peculiarly an apical phenomenon; although it may be heard better elsewhere, such exceptions are rare. It is frequently associated with a synchronous palpable and visible impulse.[1] It is an important sign in the clinic in civilian life, and is almost always of considerable gravity. During the World War, when soldiers with severe effort syndrome were gathered together, a combination of marked tachycardia and loud third heart sounds occasioned a minimization of the importance of gallop rhythm widely at variance with the appreciation of the significance of the phenomenon as seen in civilian practice. Even among patients with definite effort syndrome and otherwise normal hearts in civilian life, gallop rhythm is relatively rare; in a series of 100 such patients that I examined recently a third sound was well heard in only ten and in only one of those was the rate rapid enough for a diagnosis of gallop rhythm. In such cases differentiation is easily made from the serious gallop rhythm of heart disease in which the extra sound is generally very much louder than the usual third heart sound heard with difficulty by many physicians.

Likewise, mitral stenosis with a loud third sound and tachycardia may give rise to gallop rhythm, but not often, chiefly because the third sound is masked by the mitral diastolic murmur that accompanies and follows it.

The typical gallop rhythm is found in serious heart disease associated with hypertension, coronary disease or syphilitic aortitis, and is accompanied by congestive failure. Nephritis is not common, although it has been considered in much of the past literature to be an important factor. Gallop rhythm may be found in severe diphtheria. Angina pectoris and coronary thrombosis are common, and pulsus alternans not infrequent. Murmurs and valvular disease are uncommon, except for slight apical systolic murmurs. The heart is almost always considerably enlarged, and the sounds generally are poor. Auriculoventricular block is uncommon in spite of past theories of auriculoventricular dissociation

1. Rarely, the third sound and impulse associated with it in protodiastolic gallop rhythm may be even more prominent than the usual cardiac sounds and apex impulse, as in ten cases recently reported by Conner, seen by him in the past fifteen years (Conner, L. A.: Note on the Occurrence of an Unusual Form of Gallop Rhythm, Am. Heart J. **2**:514 [June] 1927). He writes that in these cases "the gallop sound is so loud and the corresponding palpable shock so strong as to dominate completely the cardiac signs."

Results of Observations in One Hundred Cases of Gallop Rhythm

	Type of Gallop Rhythm				
	Proto-diastolic	Presys-tolic	Systolic	Unspecified	Total
Total Cases	64	12	4	20	100
Sex:					
Male	47	7	3	15	72
Female	17	5	1	5	28
Age:					
Under 20 years	5	0	0	2	7
From 20 to 30 years	5	1	0	3	9
From 30 to 40 years	7	1	2	3	13
From 40 to 50 years	7	1	1	4	13
From 50 to 60 years	18	6	0	4	28
From 60 to 70 years	14	2	1	3	20
70 years and over	8	1	0	1	10
Etiology:					
Coronary disease	14	2	1	2	19
Coronary disease plus all complications	38	7	1	8	54
Coronary thrombosis	13	3	1	4	21
Hypertension	2	0	0	3	5
Hypertension plus all complications	30	7	1	11	49
Syphilitic aortitis	5	1	0	3	9
Syphilitic aortitis plus all complications	9	1	0	3	13
Rheumatic heart	9	0	0	1	10
Rheumatic heart plus all complications	10	0	1	1	12
Congenital	1	0	0	0	1
Uremia	0	0	0	1	1
Uremia plus hypertension	5	2	0	2	9
Irritable heart	0	1	1	1	3
Subacute bacterial endocarditis	2	0	0	0	2
Nephritis	6	2	0	4	12
Pericarditis	1	0	1	1	3
Unknown	2	1	1	1	5
Duration of Illness:					
Under 1 year	15	5	1	2	23
From 1 to 5 years	23	4	1	6	34
More than 5 years	12	3	0	1	16
?	14	0	2	11	27
Congestive Failure	42	5	1	13	61
Angina Pectoris	18	4	1	2	25
Cardiac Asthma	8	3	0	3	14
Pulse Rate:					
Under 80	4	0	0	0	4
From 80 to 100	25	6	3	6	40
From 100 to 120	24	3	1	7	35
120 and over	6	3	0	3	12
?	5	0	0	4	9
Blood Pressure—Systolic:					
Under 100 mm.	2	1	0	0	3
From 100 to 150	27	3	3	10	43
From 150 to 200	24	5	1	5	35
From 200 to 250	10	3	0	5	18
250 and over	1	0	0	0	1
Pulsus Alterans	13	5	0	3	21
Size of Heart:					
Very large	18	0	1	8	27
Moderate enlargement	23	3	1	6	33
Slight enlargement	5	6	1	4	16
Normal	1	3	1	1	6
Doubtful	17	0	0	1	18
Heart Sounds:					
Poor	34	5	1	12	52
Fair	16	5	0	3	24
Good	9	2	1	2	14
?	5	0	2	3	10
Murmurs and Valve Lesions:					
Aortic regurgitation	8	1	1	5	15
Mitral stenosis	3	0	0	1	4
Both aortic regurgitation and mitral stenosis	4	0	0	0	4
Apical systolic, loud	9	0	0	3	12
Apical systolic, slight or moderate	21	2	1	6	33
No murmurs	16	9	2	5	32
Electrocardiogram:					
Total	43	8	2	11	64
Normal	2	0	0	0	2
Auriculoventricular block	8	2	0	1	11
Intraventricular block	16	2	1	5	24

Results of Observations in One Hundred Cases of Gallop Rhythm—Continued

	Type of Gallop Rhythm				
	Proto-diastolic	Presys-tolic	Systolic	Unspecified	Total
Ectopic auricular tachycardia	2	2	0	1	5
Abnormal T wave	10	2	0	4	16
Low voltage	4	0	0	0	4
Left axis deviation abnormal	12	3	1	3	19
Auricular fibrillation	2	0	2	1	5
Ventricular premature beats alone	7	2	0	2	11
Auricular premature beats alone	2	0	0	0	2
Both auricular and ventricular premature beats	5	1	0	0	6
Nonprotein Nitrogen in Blood:					
Normal amount	8	1	2	4	15
Abnormal amount	2	0	0	3	5
Renal Function (phenolsulphonphthalein):					
Normal	4	2	1	1	8
Abnormal	5	0	0	4	9
Digitalis:					
Large amount	9	0	0	3	12
Moderate or little	33	5	1	8	47
None	15	5	3	9	32
?	7	2	0	0	9
Dead:					
Total	31	3	1	14	49
Within one week after the discovery of the gallop rhythm	3	1	0	2	6
From 1 week to 1 month	4	0	0	5	9
From 1 to 6 months	12	1	1	3	17
From 6 to 12 months	7	0	0	2	9
From 1 to 2 years	4	0	0	0	4
From 2 to 3 years	1	1	0	0	2
3 years and over	0	0	0	2	2

as a frequent cause of the gallop. Intraventricular block, almost always of the right bundle branch type, is more common, but by no means uniform, simply representing extensive myocardial disease. The heart rhythm is almost always normal, except that there are frequent premature beats. Auricular fibrillation is rare. The pulse rate is usually between 80 and 120 and rarely above or below these limits. Males more often show the phenomenon than females. The sign is one of bad omen; when occurring in the clinic it usually means death within a few years at best; there are exceptions. Digitalis therapy is apparently not related to gallop rhythm, except that improvement in the cardiac condition from its use may cause the gallop rhythm to disappear, and occasionally delayed conduction from digitalization may give rise to temporary presystolic or even, if extreme, protodiastolic gallop rhythm.

PRESENT OBSERVATIONS

A series of 100 cases of gallop rhythm observed during the last few years has been analyzed, and the results recorded in the accompanying table. Sixty-five patients from my own private practice were studied, two from that of Dr. H. B. Sprague and thirty-three from the wards and outpatient department of the Massachusetts General Hospital.[2]

2. In the study of the hospital patients, I wish to acknowledge the assistance of Dr. Seeley G. Mudd and Miss Catharine Thacher.

An attempt was made to divide them into four groups; (1) presystolic, twelve cases; (2) systolic, four cases; (3) protodiastolic, sixty-four cases, and (4) uncertain, mostly mesodiastolic, twenty cases. No great accuracy can be attached to this subdivision. The total data of the entire series of 100 cases are of considerable significance and are the basis, together with data from the literature, for the description of the typical gallop rhythm described in the foregoing paragraphs. Phonocardiograms were not taken in this series; they would be of interest in the attempt to time and to differentiate more accurately the various so-called types. Electrocardiograms were made in sixty-four of the cases.

SUMMARY AND CONCLUSIONS

1. An analysis has been made of 100 patients with gallop rhythm seen in private and in hospital practice.

2. The differentiation of these cases into types according to the time of the extra or third sound showed sixty-four apparently protodiastolic, twelve presystolic, four systolic and twenty unclassified. The exact separation of protodiastolic and presystolic types is often difficult or impossible. With rapid heart rates, as 120, the position of the third sound in diastole is practically the same, i. e., mesodiastolic, whether protodiastolic or presystolic with slower rates. The systolic type is rare and much less important apparently than the diastolic types which are about equally significant. The commonest type, namely, the protodiastolic, is probably due to the marked accentuation of the usually faint normal third heart sound.

3. Gallop rhythm is an important clinical sign in civilian practice, and is almost invariably evidence of serious heart disease. It is generally a bad prognostic sign; almost half of the 100 patients in the present series (45 per cent) are known to have died within two years of the discovery of the sign; thirty-two died within six months. A considerable number of the remaining fifty-five patients were seriously ill or dead (4) when last heard from. Cases of gallop rhythm of the protodiastolic, presystolic and unclassified diastolic types were all represented in this high mortality, but less of the presystolic than the others.

4. In the entire group of 100 cases, males were more often affected than females, in the proportion of about three to one.

5. Gallop rhythm occurred in both young and old: in sixteen patients under 30 years of age, it was more often associated with nephritis or mitral stenosis, and in the older patients with coronary disease, hypertension and syphilitc aortitis. The average age was between 50 and 60 years. One half of the patients (48 per cent) were between 50 and 70.

6. In the group of 100 cases, coronary disease alone or in combination was apparently present in 54 per cent, actual coronary thrombosis

being diagnosed in 21. Hypertension alone or complicated was present in 49 per cent, syphilitic aortitis in 13 per cent, rheumatic heart disease in 12 per cent, nephritis in 12, uremia in 10, effort syndrome alone in 3, pericarditis in 3, subacute bacterial endocarditis in 2, congenital heart disease in 1 and unknown factors in 5.

7. The duration of the heart disease before the discovery of the gallop rhythm was variable, often brief but still more often of several years' standing.

8. Congestive failure was the most outstanding characteristic, being present in at least 61 per cent.

9. Angina pectoris was a common occurrence (25 per cent).

10. Cardiac asthma occurred in fourteen cases.

11. The heart rate was usually rapid, averaging about 100. At least three fourths of the cases showed rates between 80 and 120.

12. The blood pressure was variable, the systolic being between 100 and 150 mm. of mercury in 43 per cent, between 150 and 200 in thirty-five cases, over 200 in nineteen, and under 100 in three

13. Pulsus alternans was frequently found (21 per cent).

14. The heart was considerably enlarged in 60 per cent, definitely normal in size in only 6, and doubtful in 18.

15. The heart sounds were poor in more than half the cases (52 per cent) and good in only fourteen.

16. Valvular disease was uncommon, aortic regurgitation being found alone in fifteen cases, mitral stenosis alone in four and the two conditions combined in four. Apical systolic murmurs, however, were common; loud in twelve and slight to moderate in thirty-three. There were no heart murmurs in thirty-two cases.

17. Electrocardiograms were obtained in sixty-four of the patients. Only two of these were normal. Abnormal T waves were present in sixteen, low voltage in four, abnormal left axis deviation in nineteen, auricular fibrillation in only five, ectopic auricular tachycardia in five, ventricular premature beats alone in eleven, auricular premature beats alone in two and both auricular and ventricular premature beats in six. Intraventricular block was the most common electrocardiographic abnormality found, occurring in twenty-four cases, or 38 per cent, but auriculoventricular block was surprisingly infrequent, being recorded in only eleven cases.

18. Renal function as tested by the phenolsulphonphthalein test was normal in eight and abnormal in nine of the seventeen cases so tested. The amount of nonprotein nitrogen in the blood was normal in fifteen and too high in only five of the twenty cases in which such tests were made.

19. Digitalis as a possible factor in the production of gallop rhythm was negligible, as shown by the fact that in at least thirty-two cases none had been given and in only twelve cases had a considerable amount been administered. As a matter of fact, in some cases the gallop rhythm disappeared coincidently with the clinical improvement following rest and the administration of digitalis.

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ALKALIS AND RENAL INJURY

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It has long been an established clinical fact that diuresis may be produced by the administration of alkalis.[1] M. Fischer emphasized the theoretical consideration that accumulation of water in tissues was due to an increased tissue acidity.[2] For some time therapy in nephritis and in albuminurias has been directed toward alkalinization of the urine. Post and Thomas [3] claimed decidedly beneficial results with this therapy in orthostatic albuminuria. A thorough review of this literature is unnecessary. It suffices to emphasize that in certain edematous states therapy with alkalis of various sorts has yielded a diuresis, but in certain cases has caused a dangerous exacerbation of the edema.

With the development of more accurate methods of study of the hydrogen ion concentration of the blood, and of the status of the alkali reserve in the presence of an acidosis, it has further been demonstrated that a diminished reserve of the fixed bases frequently occurs in nephritic states, with or without edema.[4] Rehn [5] believed that disturbance of renal tubular activity inhibited excretion of acids, while the excretion of alkali was dependent on glomerular function. His data are almost purely clinical and not fully controlled. An acidosis, both actual and relative, exists in acute infections [6] and anaphylactic shock. However, Hirsch has shown [7] that the nephritis which may be produced by sodium acid phosphate is not due to the acidosis. These data tend to confirm the impression that water retention is sometimes associated with an accumulation of acid. The voluminous literature dealing with the relation of the chlorides to edema is most conflicting and confusing,

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some authors [8] claiming good therapeutic results by complete and radical restriction of chlorides, and others not.

In view of the conception that water retention is associated with an increased tissue acidity, the therapeutic use of acid substances in edema, with excellent results, seems most paradoxical. Keith, Barrier and Whelan [9] produced clinical diuresis with calcium chloride, with a positive urinary calcium balance and a great increase in the sodium content of the urine. These observations have been confirmed abroad.[10] Calcium chloride has been found [11] to increase the urinary acidity and may even lead to a severe uncompensated acidosis,[12] but is still diuretic. Similar results occur with ammonium sulphate and ammonium chloride.[13] The diuretic effect is enhanced by the use of merbaphen (novarsurol).[14] Singer [15] laid particular stress on the effect of the calcium on the heart, but Segall and White [16] have demonstrated that the degree of diuresis is dependent on the degree of acidosis.

Andrews [17] has recently pointed out that the liberation of the maximum amount of water from the tissues does not occur until the plasma bicarbonate reserve has fallen to 45 per cent by volume, in normal dogs. The work of Aldrich and McClure and others [18] has shown the

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presence of a greatly increased avidity of the tissues for water in edematous and pre-edematous states, emphasizing the importance of changes in the tissues rather than merely in the kidneys. Clausen [19] and Kaboth [20] have shown that in edema significant changes occur in the surface tension and colloidal osmotic pressure of the blood. McLean [21] reviewed the chaos of conceptions concerning edema. Labbe and Violle [22] contend that edema is due to a combination of factors; namely, osmotic balance, acid-base balance, blood minerals and blood lipoids and colloids. Hamzlik [23] emphasizes the importance of the nervous apparatus in this connection, Rountree and Brown [24] have demonstrated that a true hydremic plethora with edema may be induced by the excessive administration of water, but that this has no relation to true diuresis.

Wilson,[25] in reviewing the literature, emphasizes that the mechanism of maintaining the neutrality of the body is dependent on the loss of volital carbon dioxide from the lungs, excretion of nonvolital acids and bases by way of the kidneys, excretion of some salts by way of the bowel and the normal buffer substances of the blood, chiefly sodium bicarbonate. The effect of perspiration is minor in normal persons. The loss of carbon dioxide by way of the lungs is an important factor and is directly controlled by the fact that increasing hydrogen ion concentration is an effective stimulus to the respiratory center.[26]

The mechanism by which the kidney assists in this process is the question most applicable here. Henderson's [27] and Henderson and Palmer's [28] studies have shown that the strong (actively ionized) acids are eliminated as salts, with associated depletion of the fixed metallic cations of the blood. However, ammonia, replaces these metallic cations in the urine to a great extent, and therefore tends to spare the alkali

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reserve. Previous to the work of Nash and Benedict [29] the major portion of the urinary ammonia was presumed to arise by destruction of urea in the liver. Their researches demonstrated that most of the urinary ammonia is synthesized by the renal tissue. Therefore, the acidosis associated with nephritis may at least in part be the result of the failure of proper ammonia synthesis by the kidneys. The urinary ammonia is always greatly increased in the presence of an increased secretion of acids,[30] and diminished by the administration of alkali.[31]

The normal kidney apparently can cope with excesses of alkali more readily if sufficient water is available for the solution of the sodium bicarbonate (maximum concentration is three-tenths normal).[32] The fact that alkalinization of the urine and the body requires an increased excretion of water is essentially synonymous to diuresis. Increased excretion of alkalis may be produced either by physiologic excessive administration of alkalis, or by depletion of acids, as in severe vomiting.[33]

Out of this chaos of fact and theory, a few salient phenomena are conspicuous: First, water metabolism, as exemplified by normal balance, edema or dehydration, is not solely an evidence of altered renal function as regards the excretion of the water, but is greatly influenced by physiologic and chemical conditions of the tissues as a whole. Secondly, the acid-base balance of the body is of major importance in the control of a normal equilibrium. Thirdly, the kidney, through its selective secretion of either an acid or an alkaline urine, and through its synthesis of ammonia, plays an essential rôle in the maintenance of such equilibrium. Therefore, one again returns to the kidneys for an adequate explanation of the paradoxic response in diuresis, sometimes with acid and sometimes with alkali. Renal functions are multiple. In thinking of edema and renal function one tends to emphasize unduly the function of water elimination, ignoring the renal activity in controlling the reaction of the tissue fluids.

The probable mechanism of renal secretion in connection with the control of urinary reaction has been demonstrated.[34] This was accomplished by the use of nontoxic, sensitive, indicator dyes, introduced into the circulation, and the renal tissue was studied immediately after

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removal. It was shown that in the normal animal the cellular reaction of the secreting tissue, namely, the cells of the convoluted tubules and the loops of Henle, was invariably opposite to that of the urine. If the urine is acid, the cells are distinctly alkaline in reaction, whereas with an alkaline urine an acid reaction exists in the living cells. Any increase in the alkalinity of the urine is accompanied by an increased cellular acidity. It was concluded that the reaction of the urine was determined by secretion of an excess either of acid or of alkali by these cells, with the probable retention within the cells of either the cations or the anions, resulting in the observed reversed reaction. These results are clearly interpreted in view of Donnan's equilibrium. Furthermore, in nephritic kidneys, the injured cells are acid in reaction,[34] as is the urine. Alkalinization of the urine in nephritic animals does not reverse the acid reaction of the cells, but probably increases the intracellular acidity. Similar experiments have since been carried out, using different alkalis, with the same results. However, triple calcium phosphate failed to alkalinize the urine, even in massive doses in the acute experiments.

Studies with indicator dyes in living tissues such as those already mentioned and those of Rous,[35] must be carried out as rapid, acute procedures, and be carefully controlled. The results of Rous are in part nullified by the fact that the dye was left in the tissues for a considerable time. Organic dyes, particularly the indicators, are salts, and therefore combine with the amphoteric proteins, giving false reactions if left too long in contact. For example, sodium alizarinate, if put in contact with egg albumin, will slowly show an acid reaction (alizarin), because the sodium reacts with the amphoteric protein. The actual hydrogen ion concentration is unaltered, but the indicator gives a false appearance of acidity. However, in the acute experiments referred to previously, this fact was considered.

The importance of these phenomena has been insufficiently emphasized. Since Fischer [2] and others [36] pointed out the importance of the tissues as a whole in contrast to the kidney in controlling water balance, the pendulum of attention has perhaps swung too far. After all, water elimination, and therefore control of water balance, is dependent to a great degree on proper renal secretory activity, either directly, as regards the actual excretion of water, or indirectly through the regulation of tissue neutrality by the kidneys. The actual secreting mechanism lies

35. Rous, P.: J. Exper. Med. **18**:183, 1913; Science **60**:363, 1924; J. Exper. Med. **41**:379, 451 and 739, 1925. Tissue Acidosis, editorial, J. A. M. A. **85**:519 (Aug. 15) 1925. Rous, P., and Drury, D. R.: Outlying Acidosis, ibid. **85**:33 (July 4) 1925.

36. Footnotes 18, 19 and 21.

within the renal cell, and it is important to consider the vital physiologic processes there.[37]

Recently, Hartman, Bolliger and Doub [38] in studying the physiologic process of roentgen-ray nephritis in dogs showed that during the period of acute reaction with marked albuminuria, the urine was strongly alkaline. In the absence of any systemic or metabolic disease or fever, this alkalinity may be explained only by the local inflammatory acidity of the cells, confirming the earlier experimental data. Peterson and Willis [39] have pointed out that increased hydrogen ion concentration leads to an increased permeability, whereas a diminution in permeability follows diminishing hydrogen ion concentration. This adds emphasis to the conception that alterations in the reaction of the urine have functional physiologic significance.

Excessive administration of alkali has been shown to lead to renal injury.[40] Nuzum and his associates [41] showed that long continued alkalinization caused a moderate hypertension and renal damage, but no arteriosclerosis. Addis and others [42] have been able to cause a considerable nephritis in rats by prolonged dietary alkalinization with sodium bicarbonate. The recent report of Jordan [43] has brought forth with new emphasis the problem of alkalosis as encountered in the management of peptic ulcers by the Sippy method. As has been previously pointed out by others,[44] long continued clinical use of alkalis not infrequently leads to evidence of clinical nephritis and alkalosis. Jordan points out that

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37. Stieglitz, E. J.: Am. J. Anat. **29**:33, 1921.

38. Hartman, F. W.; Bolliger, A., and Doub, H. P.: Functional Studies Throughout Course of Roentgen-Ray Nephritis in Dogs, J. A. M. A. **88**:139 (Jan. 15) 1927.

39. Peterson, W. F., and Willis, D. A.: Capillary Permeability and Inflammatory Index of Skin in Normal Person as Determined by Blister, Arch. Int. Med. **38**:663 (Nov. 26) 1926.

40. Henderson, L. J.; Palmer, W. W., and Newburgh, L. H.: J. Pharmacol. and Exper. Therap. **5**:449, 1914. Fischer (footnote 2).

41. Nuzum, F. R.; Seegal, B.; Garland, R., and Osborne, M.: Arteriosclerosis and Increased Blood Pressure; Experimental Production, Arch. Int. Med. **37**:733 (June) 1926.

42. Addis, T.; MacKay, E. M., and MacKay, L. I.: J. Biol. Chem. **71**:157, 1926.

43. Jordan, S. M.: Calcium Chloride and Carbon Dioxide Content of Venous Blood in Cases of Gastroduodenal Ulcer Treated with Alkalis, J. A. M. A. **87**: 1906 (Dec. 4) 1926.

44. Hardt, L. J., and Rivers, A. B.: Toxic Manifestations Following Alkaline Treatment of Peptic Ulcer, Arch. Int. Med. **31**:171 (Feb.) 1923. Brown, G. E.; Eusterman, G. B.; Hartman, H. R., and Rowntree, L. G.: Toxic Nephritis in Pyloric and Duodenal Obstruction; Renal Insufficiency Complicating Gastric Tetany, Arch. Int. Med. **32**:425 (Sept.) 1923. Ellis, A. W. M.: Quart. J. Med. **17**:405, 1924, Houghton, L. W.; Venables, J. F., and Loyd, N. L.: Guy's Hosp. Rep. **75**:149, 1925. McVicar, C. S.: Tr. Am. Gastro-Enterol. Ass. **27**:230, 1924.

there need be no evidence of previous gross renal damage. This is in accord with the explanation offered, namely, that the nephritis is the result, not the cause, of the alkalosis. The excessive dryness and the early rise in the concentration of the nitrogenous waste in the blood are probably the results of dehydration, or essentially synonymous, excessive diuresis, due to the irritation of acidified renal cells.

The phenomenon of alkalosis may occur without alkali therapy in those cases with obstructing ulcers and continuous secretion of acid which is lost by vomiting.[45] Normally, the blood of the portal vein has a higher alkali reserve than the arterial blood,[46] probably through the depletion of acid by the gastric mucosa. This is similar to the difference between the blood entering and that leaving the kidneys, the latter having a higher carbon dioxide combining power than the former.

On the basis of a correlation of the foregoing experimental and clinical data the paradox of diuresis by either acidification or alkalinization is open to logical physiologic interpretation. Any deviation from normal physiologic physical or chemical conditions, if the deviation is not so excessive as to be destructive, is a stimulant for activity on the part of the cells to return toward the normal environment.[47] The significant fact is that either procedure, administration of acids or alkalis, causes a deviation from the pre-existing state, and therefore acts as a renal stimulant. The result of renal stimulation is diuresis. Injured cells, already hyperirritable, are more readily influenced. In nephritis the acid renal cells are made more acid by the administration of alkalis, and it is suggested that this added insult is in part responsible for the clinical diuresis so obtained. If the original injury is severe, the additional insult, instead of being stimulating, may be destructive or injurious, with acute exacerbation of the nephritic or toxic edema, as is so often the case.[2] On the other hand, therapy with acid substances in nephritis tends to more strongly acidify the urine and to diminish the intracellular acidity, bringing the cells closer to their normal state. Such is the tentative explanation of the physiologic paradox of diuresis as the result of either acidification or alkalinization therapy, which is offered as a working hypothesis and as being food for thought along these lines. The effect of the improvement of renal function on the tissues is probably through the control which the kidney exercises over the acid-base balance of the body.

The clinical phenomena demonstrated by studies of patients with alkalosis coincide entirely with this conception. Alkalosis, by forcing

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45. Ambard, L.; Schmidt, F., and Arnovlyevitch: Bull. et mém. Soc. méd. d. hôp. de Paris **51**:75, 1927.

46. Chavit, A. J. : Arch. f. d. ges. Physiol. **214**:331, 1926.

47. Childs, C. M.: Individuality in Organisms, University of Chicago Science Series, 1915.

the secretion of a strongly alkaline urine, greatly increases the renal cellular acidity and by such irritation causes renal damage. Koehler [48] has recently pointed out that acidosis is associated with dehydration, whereas in alkalosis there is evidence of increased tissue hydration and a gain in weight. If long continued this acidification of the normally alkaline secreting cells may lead to an actual nephrosis. This probably does not occur more frequently because of the tremendous reserve of renal structure and physiologic efforts at compensation. White,[49] in a recent discussion of the rational treatment of gastric ulcer, emphasizes the fact that excessive use of alkalis is largely unnecessary. Similarly, Loevenhart and Crandall [50] suggest calcium carbonate in preference to sodium bicarbonate in ulcer therapy, because of its lesser effect on the acid-base balance of the body. This is particularly true of patients with pre-existing renal disease. The administration of large doses of alkalis in nephritis is theoretically contraindicated, even in the presence of an uncompensated acidosis. So far as is known, there is not any physiologic foundation for the use of alkalis in orthostatic albuminuria.

SUMMARY

1. Alkalinization of the urine by administration of alkalis causes an increasing renal cellular acidity.

2. This reversal of intracellular reaction is undoubtedly physiologically irritating, and thereby frequently produces a renal diuresis.

3. The diuresis resulting from acid therapy in nephritis probably results, at least in part, from physiologic neutralization of the renal secreting cells, with improvement of their functional efficiency.

4. An alkalosis, as may be produced by long continued or excessive administration of alkalis, causes distinct renal irritation and occasionally a true nephrosis.

5. Renal injury may result in impairment in the function of neutrality control and thereby affect the tissues as a whole.

6. An explanation of the paradoxic diuresis occurring after therapy with either alkalis or acids is offered.

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48. Koehler, A. E.: J. Biol. Chem. **72**:99, 1927.

49. White, F. W.: Am. J. M. Sc. **173**:629, 1927.

50. Loevenhart, A. S., and Crandall, L. A.: Calcium Carbonate in Treatment of Gastric Hyperacidity Syndrome and in Gastric and Duodenal Ulcer, J. A. M. A. **88**:1557 (May 14) 1927.

THE IODINE-STARCH TEST OF BODY FLUIDS

DEDUCTIONS FROM OVER ONE HUNDRED CONSECUTIVE TESTS OF THE EXTERNAL SECRETION OF THE PANCREAS IN DIABETES, IN DISEASES OF THE GALLBLADDER AND PANCREAS, AND IN A NORMAL CONDITION *

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Considerable interest has been awakened concerning a test for pancreatic activity which has been advanced recently.[1] Communications from different sources show its adoption as a clinical procedure for judging the condition of the pancreas by estimating the amyloclastic power of its external secretion. Doubts have arisen and the number of researches and experiences have multiplied until it seems warranted to present further data on the test.

The factors of the combining power of iodine solutions of peptone and other organic substances were known to me before the presentation of the test. So far as a solution of peptone admixture was concerned, my co-workers and I guarded against this shortly after the test was advanced, which was several months before the time of publication of the article by a procedure which I shall mention. Because the other factors could not be controlled (they were judged as insignificant), the modification of Piersol, Bockus and Shay[2] was welcomed. These observers devised a means of estimating separately all such factors as might be present, a matter which seemed most desirable, especially in that it was scientifically appealing and seemingly of advantage in making the test more accurate.

CONTROL OF RETURN OF PEPTONE SOLUTION

In the first place, one must make certain, by the use of the fluoroscope, that the tip of the duodenal tube is definitely in the duodenum. Other means of judging this are not accurate enough for the test. After the injection of 75 or 100 cc. of solution of peptone (which should be done slowly so that the solution will not flow back into the stomach), a

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* Read before the Section on Gastro-Enterology and Proctology at the Seventy-Eighth Annual Session of the American Medical Association, Washington, D. C., May 20, 1927.

1. Bassler, A.: Quantitative Test of Digestive Pancreatic Activity, Easily Applied Clinically; Tests for Volume of Pancreatic Juice and Bile Secretions, Arch. Int. Med. **35**:162 (Feb.) 1925.

2. Piersol, G. M.; Bockus, H. L., and Shay, H. H.: Value of Starch-Iodine Reaction as a Test of Pancreatic Function, Arch. Int. Med. **37**:431 (March) 1926.

jet of air is sent through the tube to drive out the solution of peptone which would be held in it by capillary attraction. The tube is then clamped off for at least three minutes; 30 cc. of sterile water is then run through the tube, air is blown through it again, and the tube is clamped off for five more minutes before aspiration for a specimen is begun.

The duodenum is capable of handling only a small amount of fluid at a time, and if this is injected too quickly, there is danger not only of fluid entering the stomach, but of its being residual in the duodenum for several minutes. The latter is a result of three factors: a delay to onward transit at the duodenojejunal angle, reverse peristalsis in the duodenum and a static state in the duodenum from quick distention, which lasts a few seconds.

When the aforementioned technic is used, a confusing return of peptone rarely occurs; this makes the procedure as suggested a satisfactory routine for clinical work, as my experience has shown. Since I adopted this method two years ago, it has been unsatisfactory in but one instance; in that case the duodenum was widely dilated from obstruction in the third part. For all practical purposes one may take it for granted that if the tube is cleared as mentioned, the fluids injected slowly, the duodenum given time to empty itself before aspiration for the specimen is begun and enough pancreatic juice obtained for testing, a specimen is secured in which the factor of the return of peptone can be eliminated.

The next suggestion that Piersol and his co-workers made was that secretions from the duodenum itself contain a diastatic ferment that would interfere with an accurate estimation of the pancreas. There is no doubt that the succus entericus from the duodenum is of considerable volume and, like all fluids of the body, must contain iodine-combining factors. Its diastatic power, however, has never been proved, and it is reasonable to assume that its combining power is not greater than that of bile or any of the other fluids of the body. At present it seems impossible to devise a means to obviate this or even to prove its presence. The starch-iodine method for work on the body fluid in estimating diastatic ferments, which I shall present later, needs considerable revision.

Doubt was then expressed concerning the practical value of the test; this is brought out more by Piersol's method of estimation, in which the iodine-combining factors which are used separately bring one back to these authors' basis of suggesting this modification and the means employed to accomplish it.

After the modification was advanced, all the returns from cases were examined by two procedures; that is, the original method was used, and then the correction of this method by separate estimation of the iodine-

combining factors and by calculation of the result accordingly. As a considerable number of fluids were to be observed, it became advisable to have a schedule so that the modification could be made more quickly; therefore the schedule given in table 1 was employed for the purpose.

Records of more than 1,400 cases in which tests were made before the modification was employed showed a striking difference in results.

TABLE 1.—*Additions of Iodine for the Bassler Test (According to Piersol et al.) in Estimating Iodine-Combining Factors in Duodenal Returns in Amounts of Centimeters of Twenty-Fifth Normal Solution of Iodine Required to Take Care of the Usual One Drop (0.05 cc.) Plus the Correction for Combining Factors*

Number of Bassler Tube	Number of Tube (Piersol et al.)									
	1	2	3	4	5	6	7	8	9	10
10	0.06	0.07	0.08	0.09	0.10	0.11	0.12	0.13	0.14	0.15
9	0.061	0.072	0.083	0.094	0.105	0.116	0.127	0.138	0.149	0.16
8	0.0625	0.075	0.0875	0.10	0.1125	0.125	0.137	0.15	0.1625	0.175
7	0.064	0.078	0.092	0.106	0.12	0.134	0.148	0.162	0.176	0.19
6	0.067	0.084	0.101	0.118	0.135	0.152	0.169	0.186	0.203	0.22
5	0.07	0.09	0.11	0.13	0.15	0.17	0.19	0.21	0.23	0.25
4	0.075	0.10	0.125	0.15	0.175	0.20	0.225	0.25	0.275	0.3
3	0.083	0.116	0.149	0.182	0.215	0.248	0.281	0.314	0.347	0.38
2	0.1	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50	0.55
1	0.15	0.25	0.35	0.45	0.55	0.65	0.75	0.85	0.95	1.05

TABLE 2.—*List of Twenty Consecutive Cases in Which the Original Bassler Test and the Piersol et al. Modification Were Performed*

Case	Bassler Original Units	Piersol Achromic Number of Tubes	Bassler-Piersol Revised (Units)
1	10	2	0
2	10	2	0
3	4	1	0
4	20	3	4
5	20	1	0
6	20	1	0
7	20	2	0
8	20	2	0
9	20	2	0
10	20	2	0
11	20	2	0
12	0	2	0
13	6	1	0
14	10	2	0
15	16	3	0
16	2	1	0
17	20	4	0
18	4	1	0
19	20	3	6
20	16	3	0

The records of the first twenty cases in which the modification was used served amply to discourage further attention to the modification (table 2).

It is apparent from a glance at the negative figures in the third column of results as compared to that in the first and from the inconsistencies in practically all of the results that the only deductions possible are either that the original method is in error, the Piersol et al modifica-

tion proving it, or that the Piersol modification is in error. Therefore, this modification was not of any value in this work and if depended on would lead only to hopeless and nullified results. I cannot explain the positive unit readings in the Piersol column in cases 4 and 19, but it must be plainly evident that these are made negative by the others in which a 20 unit reading is also found when the original method was used and no units when the modification was used. In such an indirect method of obtaining specimens for examination and in a test of this kind, there are so many factors impossible of control that the modified readings, as in cases 4 and 19, are liable to be worthless. Observations made by myself and my co-workers, however, as well as the experience of others with the Piersol et al. modification, prove that uniformly negative or low unit results are obtained, and since there was so much clinical value in the cases studied and examined by the original method, investigations were made to determine the reasons for the failure of the Piersol modification.

IODINE AS A COMBINING SUBSTANCE

Iodine is found in practically all animal, vegetable and marine life. Conspicuous with the halogens, it possesses a remarkable ability to combine readily with nonmetallic (organic) and almost all of the metals forming iodine compounds. This affinity is so strong that even with water it will combine with the hydrogen molecule and form hydriodic acid on standing. When in practically its pure form (aqueous or alcoholic solutions) and in contact with any tissues or products of them, its penetrability and combining power are well known. The products derived from the duodenum are complex, almost all of the organic materials possessing an iodine-combining power. Iodine unites with maltose and dextrose (the end-sugars of the digestion of starches and sugars) with the greatest affinity, with the dextrins somewhat less and with starch the least of all; yet iodine will detect the presence of starch in aqueous solution in only 1 in 400,000 parts, which of course works inversely when starch is used to detect the presence of free iodine.

BOILED STARCH AS A STABLE SUBSTANCE FOR TESTING DIASTASE

In its dry state, starch is a stable substance; the same may be said when it is suspended in cold water before it has had time to hydrolyze and before the granules have been more or less broken up. When the starch granule is broken by heating in water, the tegumentary portion (amidin) automatically undergoes more or less conversion into the dextrins. This is due to a chemical modification of the original starch brought about by the combined agencies of water and heat, to which changes may occur due to the enzymes which are contained in the

incasement of the starch granule and which are not destroyed by heat, or which become active again on cooling. It is true that water and heat generate a starchy substance which rather quickly changes in part into the dextrins; however, the amount of starch in such a solution that is sensitive to iodine is sufficient for a sensitive test. When a converting substance like amylopsin or diastase is present, however, the conversion is more rapid. Of especial interest is the fact that an enzyme converts only a certain portion of the starch, so that such a solution contains all of the substances from starch to the end-sugars (or the achro-odextrins), and thus the color that results ranges from the characteristic blue with iodine to no color with the dextrins and the sugars, the latter of which have the greater combining power. When small quantities of iodine are added to such a solution, the sugars and the dextrins take it up first; it is not until they are saturated that a blue color is seen on the starch, which is always present in the solution. Of further interest is the fact that the iodine-starch combination as it breaks down into the dextrins will give the iodine to the dextrin (or the sugar); thus the color will gradually fade, and unless more iodine is added, blue is not produced on the starch present.

The facts mentioned in the two foregoing paragraphs caused much confusion in the early days of the test and explain the statement made by Piersol and his associates, namely, that "a marked variation in the reaction could be produced by varying the amount of iodine added." It is strange, therefore, that since they knew this fact, they did not utilize it for recognition in the modification they suggested, and that they arranged the modification by adding these extra amounts of iodin, thus defeating the purpose they desired to achieve. Any variation in the test must not include additional amounts of iodine in the tubes used in the original test. No more than one drop of twenty-fifth normal solution of iodine should ever be added to the tubes, which subsequent data will prove further. The iodine-combining factors may be estimated separately, and with the test performed as originally planned, a method of computation may be devised that would obviate this factor of error; but this method must be one which does not necessitate the addition of more iodine to the original tubes. As will be shown presently, even then it is doubtful that any procedure which employs starch with iodine to estimate iodine-combining substances, other than enzyme activity (which has factors of error in itself), will be valueless.

ORIGINAL TEST ON SUBSTANCES OTHER THAN PANCREATIC JUICE

It may now be in order to report some of my early observations and some that have been made recently. It has long been believed that a diastatic ferment pervades the body generally and is present in all of its

fluids and tissues. With the bile of cows, Piersol and others proved that positive readings could be made on the bile with the original iodine-starch test (a matter which is confirmed subsequently). Tests were made of the various constituents in concentrations as they occur in the bile of human beings, as it was hoped that one or more of them might be identified in special ways. The results in the original and modified test, as given in table 3, prove that the main constituents of bile do not have a combining or converting power.

Various tests were then made on the bile of a number of freshly slaughtered animals and of persons on whom operations had been performed. In order to understand these figures, it must be remembered that the bile employed was always the concentrated form contained in gallbladders, in which there was much mucin and coloring matter (both of which have high iodine-combining powers); it was not like the bile

TABLE 3.—*Results in Estimating Iodine-Combining Powers of Constituents of Bile in Solutions*

Substance	Piersol et al. Achromic Tubes	Bassler Units
Cholesterin, 0.06 per cent solution	None	0
Lecithin, 0.03 per cent solution	None	0
Glycocholic acid, 0.63 per cent solution	None	0
Sodium glycocholate, 0.30 per cent solution	None	0
Sodium taurocholate, 0.30 per cent solution	None	0
Artificial bile containing parts in 100: bile salts, 0.93 per cent (consisting of glycocholate 0.63 per cent, taurocholate 0.3 per cent); cholesterin, 0.06 per cent, and lecithin 0.03 per cent, all rendered alkaline with 1.5 per cent sodium bicarbonate in a 1:5 solution	None	0

in the duodenum, especially the diluted form found in a specimen obtained during the test. There is no known test or method for the estimation of the amount of mucin; the hydrometer is valueless in maintaining an estimation on the basis of specific gravity, no matter how viscid or thin the specimen may be. It is possible that tests of viscosity would have been of some assistance, but they were not made; therefore, the only value of the unit readings was to prove that the mucin and other organic substances, because of the high iodine-combining powers, would give such high readings. The tests were made particularly to get an idea of this combining power and to compare it with that of other body fluids, to compare the results obtained with the original test and with the modification of this test and to prove or disprove a point that was raised by Lyon[3] that substances from the pancreas might be mixed with the bile while it is still in the biliary tract.

These observations prove that bile, like other body fluids, contains iodine-combining substances; again the inconsistencies between the modification and the original test are shown by the fact that normally there

3. Lyon: Personal communication to the author.

is no pancreatic juice admixture in the biliary system (because if there were, sugar would have been formed), and by two important observations which will be presented later. Other substances in fresh normal specimens were tested with the results shown in tables 5, 6 and 7.

It must be remembered that blood serum from human beings contains large amounts of organic substances; it contains blood sugar and no doubt the greatest amount of diastase, with the exception of the pancreatic juice. The high values are no doubt due to the iodine-combining substances other than diastase. Work has been done in order to

TABLE 4.—*Results in Estimating Iodine Combining-Power of Natural Biles*

Source		1 Cc. Bile, 4 Cc. 0.5% Starch Solution; Sugar Present	Piersol et al. Achromic Tube	Bassler Method Revised; Results in Units	Original Bassler Method Estimated Without 30 Minutes' Incubation; Results in Units	Bassler (Original) Estimated Without 30 Minutes' Incubation; Results in Units After Standing 20 Minutes	Original Bassler Method Estimations Made in Units After 30 Minutes' Incubation and Standing 20 Minutes
Man	A	Negative	2 tubes	0	20	20	20
	B	Negative	2 tubes	0	20	20	20
Pig	A	Negative	2 tubes	0	10	20	20
	B	Negative	2 tubes	0	8	12	20
Sheep	A	Negative	1 tube	6	8	18	20
	B	Negative	1 tube	4	10	6	10
Cow	A	Negative	1 tube	0	6	10	16
	B	Negative	1 tube	0	10	18	20

TABLE 5.—*Pancreatic (Bassler) Test of Blood Serum from Human Beings*

Case	Regular 30 Minute Incubation	Incubation 60 Minutes
1	18	20
2	20	20
3	20	20
4	18	18
5	20	20
6	20	20
7	20	20
8	20	20

estimate the proportions by precipitating the proteins and by estimating the sugar, and the suggestion is that the enzyme factor in the test is about one fourth of the figures shown in table 5.

Normal feces contain approximately 10 per cent albumin, carbohydrates and fats. The material cast off from the walls of the alimentary canal (mucus, cells, etc.) with the food albumins and sometimes sugar could easily account for these figures. A trivial amount of diastase ferment is probably contained in feces; there is no way, however, to estimate this. If it is present (this is as doubtful as its presence in urine), it does not represent more than one third of the figures shown in table 6.

The low figures shown in table 7 represent chiefly iodine-combining factors (bilirubin, cast off cells, cylindroids, leukocytes, urates and others). It is believed that if diastatic enzyme is present, which is more than doubtful, it is so trivial as not to show in the test.

PANCREATIC JUICE IN THE DUODENAL RETURN

The results obtained when employing the Piersol modification, sometimes because the proper strength and amount of iodine solution to be added have not been estimated carefully or the possibility of a peptone

TABLE 6.—*Pancreatic (Bassler) Test of Fresh Human Feces (5 Gm. Solid Feces Macerated in 10 cc. Normal Physiologic Sodium Chloride)*

Case	Piersol et al. Achromic Tubes	Bassler Revised	Bassler With no Incubation; Read Immediately	Bassler With no Incubation; Read After Standing 20 Minutes	Bassler With 30 Minute Incubation; Read After Standing 20 Minutes
1	1 tube	0	4	6	6
2	1 tube	0	0	2	2
3	0 tube	2	0	2	2
4	1 tube	0	4	8	8
5	1 tube	0	0	2	6
6	0 tube	0	0	2	4
7	1 tube	4	0	4	4
8	1 tube	0	0	6	6

TABLE 7.—*Pancreatic (Bassler) Test of Fresh Specimens of Human Urine (None Containing Sugar or Albumin)*

Case	Estimated with No Incubation		Incubation, 30 Minutes; Read After Standing 20 Minutes	Incubation, 60 Minutes; Read After Standing 20 Minutes
	Read Immediately	Read After Standing 20 Minutes		
1	2	4	4	4
2	0	2	2	2
3	0	2	2	2
4	2	2	2	2
5	2	4	4	4
6	2	2	2	2
7	0	2	2	2
8	2	4	4	4

solution admixture has not been considered, have raised the question whether pancreatic juice is obtained. The many tests that have been made, especially the usual chemical and laboratory methods for proving the presence of maltose or dextrose, have proved that, according to the presence and the amount of amylopsin existing in the specimen, sugar is promptly formed when it is added to the starch. A point of much interest in this connection is that unless amylopsin or some other type of diastatic ferment is present, irrespective of what type or how many iodine-combining factors are also present, the ferment is essential for the formation of sugars. This fact is the basis of a new method of estimating the enzyme, which up to the present has not proved satisfactory. The saccharogenic methods and Martin's recent article will be discussed later.

Two important matters have engaged my attention for the past three years. They are so revolutionary and contradictory to what has been taught and believed that they suggest reinvestigation and revision not only of the starch-iodine tests, but of the whole subject of diastatic enzymes as well.

DIASTATIC ENZYMES IN THE BODY AND THEIR ESTIMATION

Diastatic Enzymes in the Body.—The starch and iodine test has been employed from the beginning of my experiments and observations. Since the test of detecting iodine by starch and its reverse purpose was discovered by Conlin and Gaultier de Clanbry, and the technic of this quantitative test against enzymes by Wohlgemuth, innumerable analyses of body fluids have been made by them; because of the conversion of starch, they believed that diastatic ferments were present and were the cause of the change. So far as I can learn, consideration was not given to other substances in the fluid that would combine with iodine before the starch (the dextrins and sugars), to the presence of iodine-combining factors of organic nature which would have to be saturated before a blue color would result or to the automatic change that occurs in a boiled starch solution; these considerations, would, of course, seriously interfere with definite conclusions. In the light of my observations too much was taken for granted in all this work; therefore it will have to be done again more accurately.

Of all the factors liable to cause error in the starch-iodine test, especially when it is employed to test for the presence of a diastatic enzyme, the most important one is the greater affinity of dextrins and sugars for iodine as compared to that of starch, and the contained organic substances which also become saturated before starch does.

ESTIMATION OF DIASTATIC ENZYMES

The three great enzymes are the proteolytic, diastatic and lipolytic. While there are phenomena that suggest the presence of a so-called lipase, the presence of such an enzyme has never been proved, nor has it ever been isolated. In a recent article [4] it was shown that all the changes from neutral oil to the production of fatty acids can be accomplished by weak alkalis alone. As with rennin, the assumption of its existence is not justifiable, and it is possible that a true lipolytic enzyme does not exist. All proteolytic enzymes are dual in their action of conversion. This is true of the one in the stomach as well as of that in the pancreatic juice, both of which require outside activation, that of the stomach from the hydrochloric acid and that of the pancreas from a product of the duodenal mucosa (enterokinase).

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4. Bassler, A., and Lutz, J. R.: Am. J. M. Sc. **168**:869 (Dec.) 1924.

The action of all proteolytic enzymes, however, is slow, perhaps because their function is to break down a most complex substance found in native proteins. My experiments to increase the speed of this action proved that it depends on the incubation as well as on the length of time. As a general rule, this is not true of the diastatic ferments and in my work on diastatic activity with specimens from human beings and from animals, I found that in their action diastatic ferments closely correspond to a catalyzer; the action requires no time, incubation is almost unnecessary, and it occurs at any reasonable temperature, even one that is considerably lower than that of the body. If one prepares tube 1 in the original test (namely, adding 1 cc. of duodenal return to 4 cc. of the starch solution), shakes it at once and tests for sugar with Benedict's or Fehling's

TABLE 8.—*Tests of Duodenal Returns (Containing Pancreatic Juice) Showing Immediate Production of Sugar, and Comparisons of Figures Obtained Immediately and After Incubation*

Case	1 Cc. Duodenal Return, 4 Cc., 0.5% Starch Solution; Sugar Present	Immediate Units; No Incubation		Incubation, 30 Minutes;	Incubation, 60 Minutes;
		Read Immediately	Read After Standing 20 Minutes	Read After Standing 20 Minutes	Read After Standing 20 Minutes
1	+	10	20	20	20
2	+	12	20	20	20
3	+	6	10	16	20
4	Slight trace	0	0	4	4
5	+	10	16	20	20
6	+	14	20	20	20
7	Trace	2	8	8	10
8	+	4	10	20	20
9	+	2	8	14	16
10	++	14	20	20	20

solution, the sugar reaction will somewhat depend on the amount of diastatic ferment present; the test, however, is not accurate. Incubation for considerable periods of time does not cause a much greater reaction. All that is necessary is to allow the mixture to stand for a minute or two at room temperature, and definite conversion will occur.

The points made in the foregoing paragraphs evidently were not taken into consideration when a separate estimation of the iodine-combining factors was devised, and prove that there should not be modification of the original test unless some other than the starch-iodine method is found. The test as advanced is not offered as a perfect procedure, but compared to the other methods so far devised for the purpose, it is clinically the best one at present. Even with its possibility for errors, it has served in many instances both as an aid to diagnosis and as a source of suggestions for treatment. Like all laboratory methods, it no doubt is of most value when it is positive. It is a quick, inexpensive and fairly good means of estimating the activity of the pancreas; it is often of value in diabetes mellitus and in pathologic changes in the gallbladder as the concluding lists will show. Finally, as Dolley [5] has also suggested

5. Dolley: Am. J. Anat. **35**:153 (May) 1925.

in his observations, there is no basis for the belief that there is unequal secretion of the enzymes; since histologically all the cells are similar, they go through the same stages of rest and activity. Methods by which all of the enzyme activities are estimated separately fail through their own errors and are unnecessary and time consuming; generally, their use is to be discouraged. I believe that all that is necessary in order to judge the activity of the pancreas is to make estimations of the amylopsin.

PROGRESS MADE SINCE TEST WAS SUGGESTED

Mellanby [6] conducted an extensive series of experiments on the mechanism of the external pancreatic secretion. He showed that the entrance of hydrochloric acid into the duodenum does not constitute the essential stimulus for pancreatic secretion, as was the belief of Popielski,[7] but that if an extract of the pyloric mucous membrane is added, a copious secretion occurs. By analyzing this action, he seemed to prove conclusively that the effect was due to the introduction of bile into the duodenum; the acid extract of the pyloric mucous membrane caused this bile to flow and to produce an adequate reaction. The essential factor was the cholic acid contained in the bile salts, since the injection into the duodenum of pure sodium cholate which reacted adequately led to a large secretion of pancreatic juice. He also proved that mucin delays the absorption of bile salts, prevents its hemolysis of the red blood cells and prolongs the action on the pancreas. An important point discovered is that the injection of acidulated bile into the duodenum does not always cause an active pancreatic secretion, and further, that the state of alimentary activity exercises a great influence on the capacity of any given bile to evoke a pancreatic secretion. In a cat recently fed (within four hours) there was a large secretion of pancreatic juice after the injection of slightly acidified (p_H 6.5) bile into the duodenum. If, however, the cat had not been fed for twenty-four hours, the effective pancreatic stimulant would have been an injection of alkaline (p_H 8) bile into the duodenum.

Accepting Bayliss and Starling's [8] conclusions it is Mellanby's contention that secretin is important for pancreatic activity. This author shows that cholic acid is operative only in the duodenum, that its absorption is prompt, and that with its resorption the secretin passes into the blood and from thence to the pancreas, and that the immediate pancreatic stimulus is secretin carried to the pancreas by the cholic acid. In their passage through the intestinal mucosa, the bile salts absorb the secretin

6. Mellanby, J.: Lancet **2**:215 (July 31) 1926.
7. Popielski: Arch. f. d. ges. Physiol., 1901.
8. Bayliss and Starling: J. Physiol. **28**:325, 1902.

contained in the cells of the mucosa and carry it into the blood and by this means to the pancreas. In this neither the vagus nor the sympathetic nerves are operative, and the secretin in the blood is the only important factor.

Experimenting along these lines with human beings, I found that bile from man diluted five times with 1.5 per cent solution of sodium bicarbonate producted an active flow of pancreatic juice in fifteen minutes. At first I believed that the introduction of bile into the empty stomach would be irritating and perhaps cause vomiting, especially if there was acid in the stomach; this can easily be considered nonexistent, because the empty stomach (even in health) often contains bile regurgitated from the duodenum. It, therefore, was not proved to be true. If residual acid is present, the acid precipitates the bile salts and prevents absorption until it is neutralized again in the duodenum. Lecithin (which is difficult to get into solution) injected directly into the duodenum is destroyed and not absorbed in the blood. As specimens of fresh bile from human beings are difficult to obtain and to keep fresh, one dislikes to employ them because of the danger of carrying infection, and since ox bile is intensely irritating to the alimentary canal of man, the commercial salts of bile was employed. In a mixture of the glycocholate and taurocholate, the commercial salts proved to be as efficient as bile from human beings and pure sodium cholate solution. As none of the constituents of bile seems to have any iodine-combining powers, it was deemed best to use an artificial bile (in which the lecithin was omitted) the formula of which is presented in the list of artificial bile (table 3). The results thus far prove that this is a poor clinical means for stimulating the pancreas, only indifferent specimens for testing being obtained in from five to fifteen minutes after its introduction into the duodenum.

The next phase of this subject seems confusing but really is not. Mellanby has shown that bile itself is the natural stimulant for pancreatic secretion. Solutions of peptone are most active in stimulating the flow of bile, almost as active as solutions of magnesium sulphate. In early work with magnesium sulphate and solutions of peptone, the comparison showed that solution of peptone was a better stimulant to employ so far as the pancreas was concerned, magnesium sulphate being more valuable for the biliary system. In many instances when solutions of magnesium sulphate were employed, and even when the flow of bile was active, the unit figures were low; in other instances, they were irregular. It is possible that even when an active flow of bile is produced by magnesium sulphate, the salt will in some way inhibit pancreatic secretion in the short time that it takes to obtain a suitable specimen. I agree with Martin [9] that when peptone solution is employed,

9. Martin, L.: Biliary, Pancreatic and Duodenal Studies **39**:343 (March) 1927.

the A fraction may be rather uniformly employed in the test, and when magnesium sulphate is used, the B fraction may be more uniformly potent in pancreatic juice. If there is any fear that peptone admixture may be a confusing factor when irregularity of pancreatic flow is caused by the use of magnesium sulphate, properly bicarbonated artificial bile may be employed, especially since the salts of bile have no iodine-combining powers.

In a recent article by Martin, the saccharogenic method is preferred to the amyloclastic method for estimating the diastatic enzyme of the pancreas. In the early days of my work, sugar was added to the starch solution employed and a quantitative estimation by Benedict's solution was made after the solution used had been incubated and shaken three times. I could not secure uniform results with different quantities of duodenal return even when I employed buffer solutions from p_H 6.7 to 7.6, and it made little difference whether I used these in small or large quantities. In the first place, there was an activity of the enzyme with small quantities of duodenal return which in most instances would not be increased with larger quantities; in other instances there was a slight increase, but this had usually disappeared in the third and fourth tubes. In the second place, with all alkaline copper solutions used (such as that of Folin and Wu which Martin employs), the dextrose formed had 100 per cent reducing effect on the copper solution and the maltose formed only about 76 per cent. These two facts introduced a most serious variance, and even when the picric acid method of estimating sugar was employed (as in blood chemistry), this variant could not be controlled in whatever dilution it was used, although a dilution of not more than 1:500 was employed (Martin suggests 1:600). All my early work was done according to saccharogenic methods. These seemingly are more scientific and deal with a definite substance in sugar rather than with one that varies, such as starch conversion through the dextrins. The results, however, were so varying and beyond understanding and control that the amyloclastic test became the preferred one, and is the one I would recommend. In this connection I am satisfied that Martin is correct in suggesting the employment of the B fraction. If this is deficient, both the A and C should also be estimated before a final conclusion is made. I also agree with Martin that "storage of the gland," which I formerly believed occurred, is more theoretical than actual. I have learned that it often takes longer to stimulate pancreatic secretion; in a few instances the time is as long as from ten to fifteen minutes after the stimulant is introduced. This is the time in which the B fraction is obtained in an ideal performance. There are distinctly three types of pancreatic flow after stimulation: the prompt, the average and the slow. In these the highest contents of

pancreatic juice would roughly correspond to the A, B or C fractions. In my work the three fractions were kept separate. First the A fraction was examined; if this was normal, I did not proceed, but if this was low, I examined the B and C fractions. The figure expressing the units is the highest figure obtained in any one fraction; in the list of cases that follows this was the routine throughout, the fraction used not being mentioned.

CLINICAL EVALUATION OF THE PANCREATIC TEST (ORIGINAL)

For this purpose, four types of more than 100 cases in which the test was performed have been listed. In this group there was one case of sarcoma of the body and of the tail of the pancreas (which gave a 2 unit reading), an instance of pancreatic fistula following an operation for hemorrhagic pancreatitis (which gave a 6 unit reading) and one case of chronic pancreatitis (which did not give any unit reading). The unit readings were so low that they were excluded from the list. In addition to this, determinations of serum bilirubin and cholecystography were performed in groups 2 and 3; it is not essential to report these observations in this connection. The groups are as follows:

GROUP 1: This group included instances of diabetes mellitus, in which condition it is well known that disorder or disease of the pancreas frequently occurs; it was therefore deduced that if a disorder of the islands of Langerhans was affecting the quantity of the internal secretion of the gland, a more or less general disorder of the cells of the whole pancreas might exist. It was assumed that by testing the external secretion of the gland in proved cases of diabetes mellitus, clinical values of its usefulness would be determined. It may be recalled that in many instances patients with diabetes mellitus have disease of the biliary system, especially gallstones, and while none of the patients gave any suggestions of disorders in the biliary tract, the Lyon-Meltzer method of examination was employed as a check so far as this might be valuable and in no sense as a means of examination for the diagnosis of diabetes.

GROUP 2: In a small series of instances of verified biliary disease, all the patients were carefully examined at operation. The object was to note the incidence of unit values in those in whom the head of the pancreas was definitely thickened, stiffened or hardened, a matter which different surgeons variously estimate according to the results of their examination and the personal equation. It is reported that pathologic changes in the gallbladder are found in from 3 to 20 per cent of the patients who have been operated on for disease of the gallbladder. The deficiencies of the pancreatic test for purposes of diagnosis, the inconsistencies between it and the Meltzer-Lyon method of examination, and the extent to which the Meltzer-Lyon method was positive were noted.

GROUP 3: In this group was included a series of clinical cases of disease of the biliary tract; all the patients had digestive symptoms of direct or reflex type and all had localized symptoms of pain under the right costal margin with objective pain or distinct tenderness on physical examination. A careful analytical history was obtained in all cases, and a differential diagnosis was made in order to ascertain that the right kidney and the appendix were not diseased and that there was no pathologic condition in the colon. All of these patients were also studied by means of the roentgen ray, and bilirubin tests of the serum were made; unless the symptoms showed conclusively that disease of the biliary tract was present, the cases were not reported in this group. The object was to obtain an average unit reading to compare with that of the group of patients without pathologic changes in the gallbladder, and

TABLE 9.—*Pancreatic Unit and Meltzer-Lyon Test in Diabetes (Group 1)* *

Case	Diagnosis	Meltzer-Lyon Test	Pancreatic Units
1	Diabetes	Positive	8
2	Diabetes (marked)	Negative	0
3	Diabetes	Negative	4
4	Diabetes	Positive	4
5	Diabetes (marked)	Negative	0
6	Diabetes (marked)	Negative	0
7	Diabetes	Positive	4
8	Diabetes (marked)	Negative	2
9	Diabetes (marked)	Negative	0
10	Diabetes	Negative	6
11	Diabetes	Negative	20
12	Diabetes	Negative	4
13	Diabetes	Negative	20
14	Diabetes	Negative	4
15	Diabetes	Negative	8

* The pancreatic units averaged 5⅔ units (normal average, 10 units); deficiency was present in 86⅔ per cent and absent in 13⅓ per cent; the Meltzer-Lyon test was negative in 80 per cent and positive in 20 per cent.

to note the differences and inconsistencies between this method and the Meltzer-Lyon method of diagnosis; I also wished to ascertain to what extent the Meltzer-Lyon method was positive.

GROUP 4: This group contained a miscellaneous group of patients who did not show any signs of diabetes or disease of the biliary tract; they were carefully examined for these conditions before being included in the group. The object was to obtain an average unit reading which could be compared with the reading of the diabetic patients and of those with clinical types of disease of the biliary tract; it was also to judge the efficacy of the Meltzer-Lyon method of diagnosis in negative cases of disease of the biliary tract.

If a unit reading below 10 is considered positive, it is evident that the majority of patients with diabetes mellitus have a deficiency of the external as well as of the internal (islands of Langerhans) enzyme secretion of the pancreas; in this way the value of the test is manifest In cases 2, 5, 6 and 9, all readings were negative in pancreatic units; in case 8, marked hypopancreorrhea existed. In these five cases it was

interesting to note that difficulty was experienced in keeping the specimens of urine sugar-free or approximately so when the patients were placed on diets that maintained normal basal metabolism. To accomplish this, it was necessary to give these patients daily doses of insulin in addition to the specified diet. It was possible to reduce the dosage of insulin about the second or third day when pancreatic feedings of from 100 to 250 Gm. of pickled gland were given daily. There was also marked general improvement in health, strength and well-being. This was so striking (in these five cases, as well as in four others) that an

TABLE 10.—*Pancreatic Units and Meltzer-Lyon Test in Verified Diseases of the Gallbladder (Group 2)* *

Case	Diagnosis	Meltzer-Lyon Test	Pancreatic Units	Operation
1	Chronic cholecystitis	Positive	4	Cholecystectomy; stiffened pancreas
2	Chronic cholangitis	Positive	12	Gallbladder removed before tests; normal pancreas
3	Chronic cholecystitis	Positive	2	Cholecystectomy; stiffened pancreas
4	Chronic cholecystitis (with stones)	Positive	1	Cholecystectomy; stiffened pancreas
5	Chronic cholecystitis (with stones)	Negative	6	Cholecystectomy; stiffened pancreas
6	Chronic cholecystitis (with stones and ulcer)	Negative	2	Cholecystectomy; gastro-enterostomy; ulcer attached to pancreas which was firm
7	Chronic cholecystitis (with stones)	Negative	6	Cholecystectomy; stiffened pancreas
8	Chronic cholecystitis (with stones)	Negative	10	Cholecystectomy; normal pancreas
9	Chronic cholecystitis (stones and gastric carcinoma)	Positive	10	Cholecystectomy (sclerosed gallbladder) partial gastrectomy; normal pancreas
10	Chronic cholecystitis (with stones)	Negative	18	Cholecystectomy; normal pancreas
11	Chronic cholangitis	Negative	0	Cholecystectomy; stiffened pancreas
12	Chronic cholecystitis	Positive	0	Cholecystectomy; stiffened pancreas
13	Chronic cholecystitis (steady jaundice)	Positive	2	Cholecystectomy; firm pancreas
14	Chronic cholecystitis (with stones)	Negative	2-18	Cholecystectomy; stiffened pancreas
15	Chronic cholecystitis	Negative	18	Cholecystectomy; normal pancreas

* The average pancreatic units were 6½ (normal low average, 10 units); averaged stiffened pancreas were 2½ units; the pancreas was considered involved in ten of these fifteen cases (about 67 per cent) and not involved in five of these fifteen cases (about 33 per cent); the Lyon-Meltzer test was positive in seven of these fifteen cases (about 45 per cent) and negative in eight of these fifteen cases (about 55 per cent).

explanation was sought; while academic, the following explanation is worthy of consideration. It may be that in diseases and disorders of the pancreas causing the condition of diabetes, the deficiency of the enzyme content of the external secretion in some way brings about a deficient type of end-sugars for resorption; the liver cells cannot store these sugars; therefore they flow into the general blood stream and appear in the urine. These sugars can be oxidized by insulin. If, on the other hand, pancreatic substances are added to the digestion to make up the shortage in the pancreatic juice, the sugars are hydrolyzed in more complete form, and are then capable of being stored and oxidized with lesser amounts of insulin. As an argument against this, one must consider that in the feeding of pancreatic gland substances, some islands

of Langerhans are ingested; perhaps these cells contain insulin, which, when resorbed, answers the same purpose as insulin administered hypodermically.

The main point, however, is the fact that the pancreatic test was accurate as it verified known clinical facts in showing low pancreatic units in the returns. Except in cases 11 and 13, the unit contents were noticeably low or absent; even in the total unit readings, the average was only $5\frac{3}{5}$ units, almost half of the low normal (10 units). As there are types of diabetes in which a normal pancreas is found, and since both of these cases were of simple types and easily controlled by diet alone, they could be excluded from the list; this would then leave the average content of the remainder only $3\frac{5}{13}$ units. Manifestly, the returns from the duodenum in these patients contained all of the iodine-combining factors (with the exception of the enzyme that causes starch conversion in the pancreatic juice), and yet the value of the test was conclusive in the procedure as originally advanced.

There was some doubt concerning the involvement of the pancreas in case 9. The carcinoma was definitely located in the pyloric region, and there was considerable involvement of the glands. Decision on this point was difficult. In case 14 the second unit estimation represents the result of a test made fifteen weeks after operation. It is not uncommon (in the ideal case) for congestion of the head of the pancreas to subside after the gallbladder has been removed, the external secretion (and often the internal) becoming normal again. However, in this small group the average pancreatic unit is almost as low as that for diabetic patients, and the reading for those with definite changes in the pancreas is almost one fifth of the low normal figure. In all of these cases the icterus index was above 7, that of case 13 being 28 (Rosenheim's method employed). In this group, the comparison between the estimation of units and the Meltzer-Lyon method of diagnosis is interesting. The pancreatic unit estimations are not offered as a means for diagnosing disease of the gallbladder, although this test is often valuable in judging whether or not the patient should be operated on[10] rather than treated medically. It is interesting, however, to know that by the unit estimation a higher percentage of clinical value was obtained than by the Meltzer-Lyon method. The results are conclusive as to the clinical value of the test.

In this group it was decided that operation should be performed in cases 9, 14, 20, 26, 30, 31 and 34. In case 9, the patient reported marked improvement after medical treatment; it was not possible to make a second pancreatic test. Case 14 was not traceable, and in case 20 the

10. Bassler, A., and Lutz, J. R.: M. J. & Record (supp.) **122**:275 and 321, 1925.

operative risk was great, a stone being present in the pelvis of a kidney; the other kidney had been removed because of a stone, and a discharging sinus remained. There was also marked myocarditis. Following simple treatment, the patient had not had pain in the gallbladder up to the time this article was written (a period of fifteen months). In case 26 operation would have been a mistake, as when constant drainage of bile and

TABLE 11.—*Pancreatic and Meltzer-Lyon Tests in Clinical Types of Disease of the Biliary Tract (Group 3)* *

Case	Diagnosis	Meltzer-Lyon Test	Pancreatic Units
1	Chronic cholecystitis	Positive	6
2	Chronic cholecystitis	Positive	8
3	Chronic cholecystitis	Positive	4-18
4	Chronic cholecystitis	Positive	9
5	Chronic cholecystitis	Positive	6
6	Chronic cholecystitis	Positive	6-12
7	Chronic cholecystitis	Positive	6
8	Chronic cholecystitis	Negative	4
9	Chronic cholecystitis	Negative	4
10	Chronic cholecystitis	Positive	12
11	Chronic cholecystitis	Positive	6-14
12	Chronic cholecystitis	Negative	6
13	Chronic cholecystitis	Negative	6-18
14	Chronic cholecystitis	Negative	2
15	Chronic cholecystitis	Negative	20
16	Chronic cholecystitis	Negative	6-20
17	Chronic cholecystitis	Positive	20
18	Chronic cholecystitis	Negative	14
19	Chronic cholecystitis	Negative	16
20	Chronic cholecystitis (with stones)	Positive	0
21	Chronic cholecystitis	Negative	20
22	Chronic cholecystitis	Negative	6
23	Chronic cholecystitis	Positive	20
24	Chronic cholecystitis	Positive	20
25	Chronic cholecystitis	Positive	16
26	Chronic cholecystitis	Negative	2-18
27	Chronic cholecystitis	Positive	7
28	Chronic cholecystitis	Negative	18
29	Chronic cholecystitis	Negative	4
30	Chronic cholecystitis (with stones)	Positive	20
31	Chronic cholecystitis (with stones)	Positive	20
32	Chronic cholecystitis	Positive	2-12
33	Chronic cholecystitis	Negative	20
34	Chronic cholecystitis	Positive	2
35	Chronic cholecystitis	Negative	10
36	Chronic cholecystitis	Positive	6
37	Chronic cholecystitis	Positive	2-10
38	Chronic cholecystitis	Positive	20
39	Chronic cholecystitis	Negative	8
40	Chronic cholecystitis	Positive	6

* The average number of pancreatic units in all was 9¾: the unit readings were positive as to the pancreas in twenty-five cases and negative as to pancreas in fifteen cases; the Lyon-Meltzer test was positive as to the gallbladder in twenty-three cases and negative in seventeen cases. When two figures occur in the column giving the units, the first was obtained before and the second after the time of treatment.

treatment were instituted, the patient made a good symptomatic recovery, with restoration of pancreatic function. In cases 30 and 31, the patients were not given any treatment to speak of; they have been comparatively free from symptoms and therefore have refused operation. In case 34, the patient had an extensive pulmonary tuberculosis, and the value of an operation was questionable.

The average unit readings of the whole group was 9¾; fifteen cases in which the units were normal or above and twelve in which they were of the highest range possible were included in this group. The test in 62.5 per cent of this group showed that diseases of the gallbladder existed which affected the pancreas; it showed that only 37.5 per cent were free from these conditions. In the cases Deaver reported, the pancreas was involved in 4.6 per cent of the instances of disease of the gallbladder, and in practically one half of the cases glycosuria was present before operation. These figures for the pancreatic test are strongly suggestive of the fact that in diseases of the gallbladder functional disturbances of the pancreas represent a much higher incidence than this, and that some of the congestive or hyaline types of pathologic conditions of the acni are not palpable at operation. It is well known that glycosuria as a symptom of pancreatic disease is not a dependable clinical symptom, because most often it does not exist in general disease of the gland; if it does, it is usually transient. It is interesting to note in this group that the unit figures are even more valuable clinically in this indirect means of estimating pathologic changes in the gallbladder than in the more direct means of the Meltzer-Lyon method. The inconsistencies between the two in individual cases are not sufficient for me to make any deduction from, especially as disease of the biliary system may exist without pancreatic involvement or change in function. It seems certain, however, that in disease of the biliary tract the pancreas should be examined for additional information, especially in helping to decide which patient should be operated on and which should receive medical treatment. Improvement has been noted in a considerable number of cases of chronic cholecystitis in which the patients have received treatment, especially in cases in which the patients did not have gallstones.

Case 4 was interesting in that there was a transient glycosuria, with a blood sugar averaging 0.17 per cent on three occasions. This was an instance of potential diabetes, although when the patient ate the average kind and amount of food the specimens of urine were more often negative than positive when tested for sugar, and when positive, the quantity of sugar was always below 0.5 per cent. In case 5, numerous Welch bacilli were found, and the feces were gram-positive when the patient was eating a normal test diet (saccharobutyric toxemia). This type of intestinal infection usually causes the blood sugar to become higher than normal; this is sometimes true also of the icterus index. In this patient, both were above normal. Case 11 is excluded because the general health and weight of the patient improved, and the pancreatic units, which were not much below normal in the first instance, soon increased. In case 13, it is possible that the pancreas was involved; operation was not performed. In case 26, the patient was operated on; a great many adhesions were present, which originated in the first part of the duodenum spread

in all directions. The head of the pancreas was felt with great difficulty, and it was impossible to state whether or not it was firmer than normal. The slight lowering in the pancreatic units in case 33 is not accounted for, and I cannot offer any suggestions; case 35 was probably an instance of chronic cholecystitis, but there were not enough clinical symptoms to warrant this diagnosis. A marked chronic gastritis existed, with a

TABLE 12.—*Pancreatic and Meltzer-Lyon Tests in Nonbiliary Tract Disease (Group 4)* *

Case	Diagnosis	Meltzer-Lyon Test	Pancreatic Units
1	Migraine	Negative	14
2	Redundant colon; stasis; chronic constipation	Negative	12
3	Arthritis	Negative	20
4	Hypopituitarism; hyperglycemia	Negative	4
5	Saccharobutyric toxemia; chronic diarrhea	Negative	4
6	Infected tonsils; chronic gastritis	Negative	10
7	Colonic stasis; menopause	Positive	15
8	Saccharobutyric toxemia	Negative	20
9	Ptosis	Negative	20
10	Colitis; ptosis	Negative	18
11	Ptosis; debility	Positive	8-20
12	Gastric ulcer	Negative	14
13	Gastric cancer	Positive	6
14	Cardiospasm	Positive	20
15	Neuritis; toxemia, indol type	Negative	8
16	Colitis	Negative	20
17	Subacute appendicitis	Negative	20
18	Colitis; toxemia, indol type	Negative	18
19	Toxemia, indol type	Negative	18
20	Ptosis; toxemia, indol type	Negative	20
21	Arteriosclerosis; nephritis	Negative	20
22	Toxemia, indol type	Negative	20
23	Hanot's biliary cirrhosis	Positive	20
24	Ptosis	Negative	20
25	Ileocolonic stasis	Negative	10
26	Duodenal ulcer	Negative	4
27	Toxemia, indol type	Negative	10
28	Toxemia, indol type	Negative	20
29	Menopause	Negative	20
30	Saccharobutyric toxemia; colonic stasis	Negative	20
31	Saccharobutyric toxemia	Negative	20
32	Psychoneurosis	Negative	20
33	Colonic stasis; epilepsy; debility	Negative	8
34	Ptosis; colonic stasis; uterine fibrosis	Negative	14
35	Chronic gastritis; chronic cholecystitis (?)	Positive	8
36	Ileocolonic stasis; toxemia, indol type	Negative	14
37	Gastroduodenitis	Negative	20
38	Chronic gastritis	Negative	20
39	Chronic appendicitis; colonic stasis	Negative	20
40	Hemorrhagic gastritis; ptosis	Negative	16

* In all cases the average pancreatic units were 15+; below normal in seven cases (except case 7) and above normal in thirty-three cases (except case 7); the Meltzer-Lyon test was positive in six cases and negative in thirty-four cases.

history of three attacks of catarrhal jaundice which had extended over a period of seven years. Even with these more or less doubtful cases considered in the reckoning, the pancreatic units were 15 plus (the normal range being between 8 and 14, or 10 taken as the low normal), and twenty-nine cases were above 14 in unit reading. In these cases of disease of the gallbladder in which the pancreatic unit test was negative (omitting cases 4 and 35 in the calculation), the Meltzer-Lyon test was positive in 4, or 10 per cent.

These figures of pancreatic units when compared with lists numbers 1, 2 and 3, strongly suggest the clinical value of estimating pancreatic efficiency in diabetes and in diseases of the gallbladder and of the pancreas, as well as the value of the original test. Inconsistencies which are not explainable will be encountered, but when clinical diagnoses of diabetes and of disease of the gallbladder and of the pancreas can be made, this test adds information that is often of signal service when it is positive.

CONCLUSIONS

A technic is described to obviate the possibility of peptone admixture in the specimen.

The Piersol, Bockus and Shay modifications to estimate the iodine-combining factors other than those that occur as a result of the action of the enzyme on starch solutions are of no practical value and nullify the original test.

Sugars, dextrins and animal substances in solution have a greater combining power for iodine than has starch when present in the same solution, and it is not until these have been saturated that the characteristic blue color of the iodide of starch is seen.

Boiled starch is not a stable solution and hydrolyzes considerably after cooling. This is accomplished by simple chemical change and also by the action of an enzyme contained in the encasement of the starch granule. In the performance of the original test, this need not be accounted for. To estimate this, as well as all of the iodine-combining factors contained in body fluids, a procedure would have to be devised with this test which would not permit an addition of iodine greater than 1 minim (0.06 cc.) of the twenty-fifth normal solution suggested in the original test.

Constituents of bile in solution, singly or in combination, have no conversion power on starch, nor do they contain iodine-combining factors. Natural bile from animals is heavy in combining factors, the same being true of blood serum, feces and urine of human beings. The latter fact has not been taken into consideration in tests for diastatic enzymes in the past, and thus the presence and amounts of such enzymes have been too much taken for granted.

Pancreatic juice is present in duodenal returns and does not mix with bile while it is in the biliary tract.

The action of amylopsin is that of a catalyzer, and incubation, time and heating to body temperature are usually not necessary. The end-products of its action on boiled starch are sugars, mostly maltose, and considerable dextrose.

Dissociation of the pancreatic enzymes does not occur in disorders and diseases of the gland. If amylopsin is deficient, there will also be a lack of trypsin.

As is true of rennin in the stomach, there is much doubt that a ferment called lipase exists in pancreatic juice.

Mellanby's physiologic observations on bile salts, a stimulant that causes a flow of pancreatic juice, are confirmed. As artificial bile has no iodine-combining power, it may be employed as a poor substitute for peptone (and also magnesium sulphate) for specimens of pancreatic juice. With the proper technic, however, peptone solution is the most satisfactory and can also be used for specimens of bile. For the pancreas, magnesium sulphate is often too variable for testing purposes.

In making the test, employ bile fraction A. If this is low, test fraction B, and if this is low, fraction C. The efficiency of the pancreas is expressed in the one that gives the highest number of units.

The amyloclastic is superior to the saccharogenic testing methods for clinical work. It is simpler and far more accurate.

The original test is of value in diabetes mellitus, both in diagnostic and therapeutic ways. It helps in the understanding of true pancreatic disease. A digestive reason for diabetes is presented, and when the test is definite, it shows when pancreatic feedings should be employed; the dosage of insulin may then perhaps be reduced or discontinued.

A series of instances of verified diseases of the gallbladder is presented in which the test was of diagnostic value and helpful in differentiating the operative from the medical type of case, a matter of no small moment in chronic cholecystitis.

A series of clinical types of disorders of the gallbladder is presented in which the test was of value. These, with the foregoing and the subsequent group, show the relative value of testing the pancreas. They also suggest the limited value of the Meltzer-Lyon method in diagnosing these disorders.

I believe that it is advisable to employ this test in clinical work and in the way it was originally proposed. Unlike most laboratory tests that are of value only when positive, it also has a value when negative. It has been a distinct help in my work, and on not a few occasions has it cleared up a doubt or given a suggestion that was well worth while.

DISCUSSION

DR. HARRY SHAY, Philadelphia: The disparity between the physiologic importance and the low level of clinical information regarding the pancreas is so marked that any test accurately determining its functional activity is of value. However, any clinical functional test must satisfy at least three postulates: (1) accuracy, (2) simplicity of technic and (3) test function only of organ concerned. I do not question the accuracy of the author's work; I do not doubt the simplicity of the test, but I should like to question its integrity in testing only the function of the pancreas. There is no doubt that dilution factors from sources other than the pancreas must be considered, and it cannot be denied that these dilution factors must vary at different times. More important, however, is the question whether the enzyme which is being tested for originates solely in the

pancreas. As early as 1876, Grutzner showed that extracts of duodenal gland substance from various animals showed evidence of a diastatic ferment. This was confirmed by Mendeldorf and Glaesner, and, in 1924, by Bergman, Dukes and Yarlborough. Using the method of preparation of the last named investigators, I found evidence of a diastatic ferment in the extracts from the mucosa and submucosa of the duodenum shortly after the death of a patient. It, therefore, seems improbable that a pancreatic test based on the diastatic ferment as obtained through the duodenal tube can be of great value.

Dr. Bassler indicated that there was no necessity for the modification I suggested. I did not hear any mention of the absorption factor of peptone or duodenal fluid. While it is true that the bile salts did not show any absorption factors, bile, itself, did. I would like to know how Dr. Bassler accounts for this absorption in the reaction involved in the test for the amylolytic ferment. As strong a case can be made against the value of a pancreatic test based on the determination of pancreatic lipase. While the presence of a gastric lipase is not settled, many physiologists agree that there is such an enzyme. The addition of gastric secretion to the duodenal contents occurs at many stages in the collection of duodenal material for examination. According to Starling, gastric amylolysis is greatest at the beginning of gastric digestion when concentration of hydrochloric acid has not reached a high degree. Is it not possible, therefore, that the activity of gastric lipase may be enhanced when it gets into the duodenum, a factor which cannot be ruled out in any of the pancreatic tests based on determination of lipase? Of the three enzymes, it remains for trypsin to supply the bases for a pancreatic test which is dependent on determination of enzyme. My colleagues and I are at work on such a test, but, unfortunately, we have not had sufficient experience with it to make any report.

Dr. Frank Smithies, Chicago: It is questionable whether the function of the pancreas can be judged by the estimation of one ferment. I am not saying this without experience. Physiologists who have worked with pancreatic fistulas or direct catheterization of the ducts have shown that the several ferments may vary at different times, under different stimuli and during different periods of the ordinary daily cycle, and that variations occur not only with respect to total output, but in the qualitative factor. But if one happens to be so excellent a clinician as Dr. Bassler is, I have no doubt that the results obtained by the estimation of one ferment are a certain guide in the diagnosis of disease. Personally, I should not be satisfied with his test, as a test to be depended on. A few years ago, using the Gross-Fuld-Wohlgemuth method, I performed many hundreds of tests to estimate pancreatic ferments. In practically all instances, I could demonstrate amylase in "normal" quantity, whereas other ferments were often lacking. It happened that at that time the "discovery" of a peptid-splitting "enzyme" in saliva was announced. I investigated this at the time that I was working on pancreatic ferments. Finally, I showed that if the extracts were sterilized before the ferment test was applied, practically all of these so-called "ferments" disappeared. The whole picture of this constant amylolytic activity supposedly due to the pancreas could be mimicked by inoculating sterile extracts with the organisms common to the mouth, throat and stomach. Hence, it would appear that much of the amylolytic "ferment" activity of the pancreas is due to nothing more than ordinary starch conversion by bacteria present in nonsterile extracts.

Dr. Anthony Bassler, New York: I did not offer this test as an accurate one, and I make no such claims for it today; yet as the years have gone by my co-workers and I have become more convinced that the test has clinical value

Accuracy in this field of work is difficult. When one thinks of all that happens, the stimulation of the biliary system, the gallbladder, the liver, the pancreas and the associated phenomena that occur in the initiation of digestion, one can see how difficult it is to come to any definite conclusion. I have grave doubts about the possibility of a dye method being devised to test the efficiency of the pancreas. I should be delighted to have it occur, but it looks impossible to me. We did not work on the absorption factors of peptone and duodenal juice. We figured that the average peptone output of the stomach is approximately 5 per cent. We simply estimated against that in the beginning of the work. As we have never been able to acquire a specimen of duodenal juice, except from animals at autopsy and in extracts, we do not know what that factor is. If one mixes neutral fat with a weak solution of sodium carbonate, which is the salt in pancreatic juice, one can see, with the microscope, every phenomena of fat digestion that is known. I have grave doubts that a ferment known as lipase or that the so-called rennin in the stomach really exists. Formerly, in 100 cholecystectomies performed for chronic cholecystitis there were 51 per cent of recurrences. We came to the conclusion that we were not selecting operative material wisely enough when selection was based on the intensity of the symptoms and the length of history. We then resorted to this method. If I were a patient with chronic cholecystitis and if I felt miserable from it, I would want somebody to test my pancreas in this way. I question very much whether I would permit myself to be operated on unless the output of the pancreas was low. If the output is low and we know that there is a cholecystitis, one can advise operation. Since we have adopted that policy, there have been only four recurrences in about sixty in which cholecystectomy was performed. This was accomplished on the basis of the test alone.

PERITONITIS

III. ACTIVE IMMUNIZATION AGAINST EXPERIMENTAL B. COLI PERITONITIS *

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In a previous communication,[1] the difficulties involved in the production of peritonitis and especially of fatal peritonitis were pointed out. It was found [2] that in dogs the intraperitoneal injection of virulent colon bacilli suspended in gum tragacanth always produced peritonitis which was invariably fatal. The purpose of this investigation was to determine the possibility of inducing active immunity against this type of fatal peritonitis.

EXPERIMENTAL WORK

Immunization with B. Coli Communis by the Peritoneal Route.—Twelve dogs were injected intraperitoneally with twenty-four hour cultures of *Bacillus coli-communis* in 0.9 per cent sodium chloride. In all these experiments *B. coli-communis* 300 [3] was used. Four injections were given, the intervals between successive ones being three days. The initial dose consisted of the saline washings of one agar slant, and the remaining three doses of two, three and four agar slants, respectively.

Nine of the twelve animals were injected with living and three with killed bacteria. Seven of the nine injected with living bacteria received a peritonitis-producing intraperitoneal injection of *B. coli* in gum tragacanth ten days after the last immunizing dose. The remaining two animals were injected with the bacteria in gum tragacanth four months after the last immunizing dose. The peritonitis-producing dose consisted of three agar slants of *B. coli* 300 in 40 cc. of a 2.5 per cent suspension of gum tragacanth in 0.9 per cent sodium chloride. The nine animals survived.

The three dogs which received immunizing doses of killed bacteria (by heating for one hour at 56 C.) were given the peritonitis-producing intraperitoneal injection fourteen days after the last immunizing dose. The three animals survived.

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* From the Department of Pathology, Western Reserve University School of Medicine.

* Aided by a grant from the American Medical Association.

1. Steinberg, B.: Am. J. Path. **2**:415, 1926.

2. Steinberg, B.: J. Exper. Med. **42**:83, 1925. Steinberg, B., and Goldblatt, H.: Studies on Peritonitis, Arch. Int. Med. **39**:446 (March) 1927.

3. Steinberg, B., and Ecker, E. E.: J. Exper. Med. **43**:443, 1926.

Six nonimmunized control dogs that received similar peritonitis-producing doses of *B. coli* in gum tragacanth succumbed in less than twenty-four hours. Autopsy of these animals showed severe hemorrhagic serofibrinous peritonitis.

Two additional dogs were immunized by the peritoneal route. Ten days after the last immunizing dose, one animal was given intravenously one-quarter slant and the other one slant of living *B. coli* 300 in 5 cc. of 0.9 per cent sodium chloride. Both animals survived.

Of two nonimmunized control dogs, one received intravenously one-quarter slant of living and the other one-quarter slant of killed *B. coli* 300 in 5 cc of 0.9 per cent sodium chloride. Both dogs died. The control animal injected with living bacteria died in three days, and at autopsy showed many abscesses in the myocardium of both ventricles. Smears and cultures of the abscesses showed *B. coli.* The dog injected with killed organisms died in twenty-four hours, and autopsy revealed only severe cloudy swelling of the kidneys, liver and myocardium.

Immunization with B. Coli by the Subcutaneous Route.—Three dogs received subcutaneous immunizing doses of living *B. coli* in saline solution in similar quantities and at the same intervals as did the dogs that were immunized by intraperitoneal injections. Two of these animals were given the peritonitis-producing intraperitoneal injection ten days, and one, thirty days, after the last immunizing dose. The three animals survived.

Three nonimmunized control dogs died in less than twenty-four hours following the peritonitis-producing dose. Autopsy showed hemorrhagic serofibrinous peritonitis.

Immunization with Staphylococcus Albus by the Peritoneal Route.—Three dogs were given intraperitoneal injections of twenty-four hour cultures of *Staphylococcus albus* in 0.9 per cent sodium chloride. Four injections were given three days apart. The initial dose consisted of the saline washings of one agar slant, and the remaining three doses, of two, three and four agar slants, respectively. Ten days after the last injection of staphylococcus the dogs were given intraperitoneal injections of a peritonitis-producing dose of *B. coli* 300 suspended in gum tragacanth. The three animals died in less than twenty-four hours. Autopsies revealed the usual hemorrhagic serofibrinous peritonitis.

SUMMARY AND CONCLUSIONS

Active immunity which lasts at least four months can be produced in dogs against fatal *B. coli* peritonitis.

This immunity can be induced by the subcutaneous as well as by the peritoneal route.

Because the subcutaneous route is effective, and because the peritoneal route also protects against a lethal intravenous injection of *B. coli*, the immunity induced is considered to be of a general nature, at least in part.

Immunization with staphylococci did not protect against fatal *B. coli* peritonitis.

BLOOD VOLUME IN EDEMA OF GLOMERULAR NEPHRITIS AND NEPHROSIS *

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The pathogenesis of edema of renal origin is concerned with changes in the blood, vessels and tissues. A review of the literature on the subject is confusing and unsatisfactory. Bright asserted that the depletion of albumin in the blood changed the physicochemical balance and edema resulted. Later Senator suggested the vascular element, and in recent years Fischer has implicated the tissue cells in the genesis of edema. The part played by the blood has interested many observers, but the exact significance of its volume in this connection has not been clear. The following brief excerpts from Loeb's [1] review of the subject of edema depict the prevailing confusion:

Volhard [2] stated that in acute glomerular nephritis with edema there is no dilution of the blood, while without edema there may be dilution. In the latter, because of the renal block, water is retained in the blood; in the former, water and salts are retained in the tissues. He also asserted that in anuria without edema there is dilution of the blood. Volhard interpreted dilution of the blood, or, as he designates it "polyemia," as not constantly followed by edema of the tissues, but caused by renal insufficiency and retention of water in the blood. Reiss [3] stated that in edematous cases there is hydremia; this term, according to his usage, implies increased volume of blood (hydremic plethora or polyemia). Nonnenbruch [4] did not find constant relationship between renal edema and polyemia (increased volume of blood). Loeb believed that transitory polyemia and hydremia may precede edema of the tissues, and that when diuresis occurs, a similar transitory condition will take place. Loeb stated that it is assumed that plethoric conditions of the blood occur in acute glomerular nephritis and that a hydremic plethora also occurs in

* From the Division of Medicine of the Mayo Clinic and the Mayo Foundation.

1. Loeb, Leo: Edema, Medicine **2**:171, 1923.

2. Volhard, Franz; and Fahr, K. T.: Die Brightsche Nierenkrankheit, Berlin, Julius Springer, 1914.

3. Reiss, quoted by Loeb (footnote 1).

4. Nonnenbruch, W.: Ueber extrarenale Odemgenese und Vorkommen von konzentriertem Blut bei hydropischen Nierenkranken, Deutsches Arch. f. klin. Med. **136**:170, 1921.

cardiac edema. Frey [5] observed this increase in nephrosis; Widal [6] observed it in chronic nephritis which preceded or accompanied the edema. Loeb criticized the methods on which the foregoing conclusions were based. Widal used the refractometric method, and with low values for the serum proteins, assumed the existence of polyemia (increased volume of blood due to fluids). Likewise fluctuations or changes in the percentage of hemoglobin and erythrocytes have been assumed to be due to dilution phenomena.

The data in the literature relative to changes in the volume of the blood are largely valueless because of the lack of a method for determining the volume of blood and of plasma. Changes in volume have been estimated on the basis of percentage of changes in single constituents. Percentage changes in the serum proteins do not necessarily indicate changes in the absolute volume of the blood or plasma. Similarly, variations in the percentage of hemoglobin and erythrocytes may reflect absolute and not percentage decreases. Conclusions with regard to the status of the volume of blood and of plasma in disease were impossible until a clinical method for its determination was forthcoming.

NOMENCLATURE [7]

The following terms for different volumes of blood have been suggested: "normovolemia" for a normal volume, "hypervolemia" for an

5. Frey, quoted by Loeb (footnote 1).

6. Widal, F.: Die Kochsalzentziehungskur in der Brightischen Nierenkrankheit; Differenzierung der Chloruraemie und der Azotaemie, Verhandl. d. Kong. f. inn. Med. **26**:43, 1909.

7. On etymologic grounds, objections have been raised to the proposed terms. The first objection is to the hybrid derivations of the Greek and Latin words. Current usage has led to the acceptance of words of like derivation, such as hypertension and volumetric. Objection has also been raised to the use of the derivative "vol" rather than "volum," but the use of the entire root creates a word lacking euphony, and so the shorter form has been used. The third objection has been directed against the policy of coining additional words. To state one man's opinion, "Why clutter up our already overburdened vocabulary?" This attitude is not justifiable when available terms are not at hand. There are no terms to indicate decreased volume of blood, while those in usage to designate increased volume are ambiguous and not descriptive. Hydremia, according to Dorland's dictionary, is "A condition in which there is an excess of the fluid portion of the blood." This does not implicate an increase in the total volume, as the fluid may be increased with a small volume of blood. It would be necessary to state that the increase was absolute and not percentile. Polyemia, according to this authority, is "plethora," or an "increase in the volume of blood." The increase may be due to either cells or fluid, or both. "Hydremic plethora," according to current usage, would indicate a large volume of blood, due chiefly to the increase in fluid. Anhydremia is a "deficiency in the fluid portion of the blood." No volume status is implicated in this definition, as the volume may be

(Footnote continued on following page)

increased volume and "hypovolemia" for a decreased volume. The three major states of volume, normal, increased and decreased, are subject alike to three possible variations, depending on the ratio as cells to plasma or cell volume to plasma volume and are designated as "simple," "oligocythemic" and "polycythemic." Chart 1 shows the nine theoretical variations in the volumes of blood and of plasma and their corresponding clinical states.

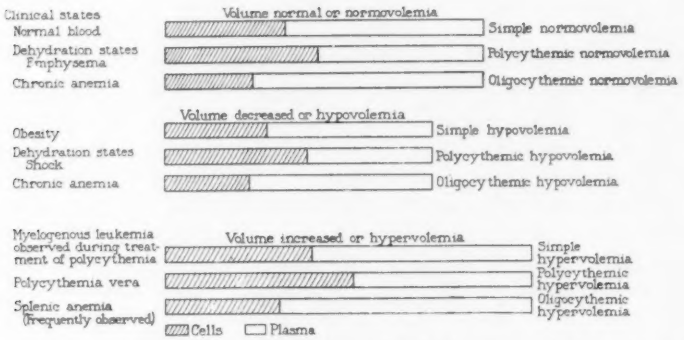

Chart 1.—Diagrammatic representation of possible states of the volume of blood, according to body weight, with different cell to plasma relationships.

METHOD

In recent years, two methods have been described for the clinical determination of the volume of blood, the carbon monoxide and the dye. The dye method of Keith, Rowntree and Geraghty,[8] has proved practical,

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normal, increased or low, and the fluid portion relatively decreased. Oligemia, olighemia and oligohemia are synonymous, meaning "a deficiency in the amount of blood in the body;" there is nothing to indicate whether the decrease is due to a relative or to an absolute diminution of fluids or of cells or both. In other words, a terminology to indicate the volume status should include information not solely of the blood mass, but also of the volume of the plasma and cells, as both may be normal or abnormal. The existent terms relative to quantity of blood are inadequate and ambiguous and were coined at a time when the volume status of the blood, plasma and cells did not enter into consideration. If one attempts to describe the volume status of the blood, plasma and cells without a concise terminology, a large number of words are necessary. For example, to describe a condition of increased volume of blood and anemia, the following definition is necessary: an increased volume of blood with a decreased ratio of the volume of cells to the volume of plasma. According to the new terminology, this would be oligocythemic hypervolemia. As the volume of the blood, cells and plasma are shown to vary in diseased states and are probably important in the correct physiologic interpretation of basic disturbances in some instances, a concise, accurate group of terms is necessary. Therefore the proposed nomenclature is offered.

8. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547 (Oct.) 1915.

and its inherent errors are known. The criticisms of the dye method have been summarized and discussed in a current publication. After further experimental work, and a larger clinical experience, we feel that most of the objections raised are invalid, and that the method is sufficiently accurate to determine the volume of the circulating plasma and blood in health and in disease. Sufficient work has been carried out in normal subjects to show that the volume of the blood and plasma is maintained within rather narrow limits. Variations in values are shown in many diseases; these changes correlate closely with the anticipated variations, and are of sufficient magnitude to indicate that they cannot be accounted for by defects in the method.

The method used in our determination is essentially that of Keith, Rowntree and Geraghty, except that congo red instead of vital red was used because of its availability. The optimal time for withdrawal of blood after the injection of the dye was between three and six minutes. The loss of dye from the blood within this time is negligible.

We have found no basis in fact for Lindhard's [9] criticisms of the method. His criticisms of congo red have been carefully investigated by a series of experiments which will be discussed in detail in a subsequent publication. Suffice it to state that we were not able to substantiate his claims concerning the adsorption of the dye by the erythrocytes. Concentration from twenty to thirty times that used in the method is necessary before demonstrable amounts are taken up by the cells. His other criticism of the method relating to the variations in the concentration of the dye in the different veins and the effects of exercise on the volume of blood have been considered, and his experiments have been repeated. Our work indicates that variations in the values of the volume of blood based on determinations made simultaneously on the right and left arms do not exceed 2 per cent, a variation less than the accepted error in the method. While exercise may introduce an extraneous factor, which, like other factors, may influence the volume of the blood, it does not enter into consideration of the volume of the blood under basal or resting conditions, in which our comparative studies have been made. Because of the difference in the result of Lindhard's experiments and our own, we must conclude that differences exist in the various dye preparations on the market. We have used the American made brand of congo red purchased in the open market, and have tested it in animals for toxicity, and for abnormal absorptive properties on human blood in vitro before employing it in our clinical studies.

9. Lindhard, J.: A Dye Method for Determining Blood Volume in Man, Am. J. Physiol. **77**:669, 1926.

Bennhold's [10] observation of the rapid disappearance of congo red from the circulation in cases of pure nephrosis and amyloid disease has been confirmed by Bookman and Rosenthal [11] and by us. Bookman and Rosenthal noted a loss of from 47 to 55 per cent of dye in one hour. In four determinations in three cases of nephrosis, we have seen a loss of from 11 to 36 per cent in one hour, as contrasted with Bennhold's 11 to 30 per cent for normal subjects. His data do not show whether the loss is more rapid within the three to six minute interval. In four cases of nephrosis, dye appeared in the urine within ten minutes after injection, but the rate of disappearance of the dye in the serum for the three, four and six minute intervals has averaged only about 1.5 per cent greater than the normal time of disappearance (table 1).

Normal Values by the Dye Method.—The normal values for the volume of blood under resting conditions have been compiled from Keith, Rowntree and Geraghty's data on eighteen subjects and from those on

TABLE 1.—*Volume of Plasma in Nephrosis with Loss of Dye in the Urine Within Ten Minutes After Injection*

Case	Two Minutes*	Three Minutes	Four Minutes	Six Minutes
1	100	100	103	103
2	100	97	100	100
3	100	100	103	103
4	100	100	100.2	100.2
Twenty†	100	100.6	101.5	101.4
Normal subjects		±0.5	±0.6	±0.5

* The value for the two minute period is arbitrarily given as 100. The values for other periods represent the percentage variation from the two minute period.
† Mean values with probable error.

thirty-eight normal subjects of our own series. The ages varied from 15 to 70 years. The mean or average normal volume of blood, calculated for each kilogram of body weight, was 89.1 ± 0.6 cc. or $3,383 \pm 33$ cc. for each square meter of surface area. Ninety-eight per cent of our normal volume values varied between 70 and 100 cc. for each kilogram. The mean volume of plasma was 50 ± 0.5 cc. for each kilogram of weight or $1,973 \pm 20$ cc. for each square meter. Ninety-six of the values of the volume of normal plasma varied between 40 and 60 cc. Determination of the correlation coefficients by statistical methods indicates a slightly higher relationship of the volume of blood to surface area than to the weight of the body in the group with normal weight. In

10. Bennhold, Herm: Ueber die Adsorptionsfähigkeit der Serumkolloide tubulär Neirenkranken gegenüber Farbstoffen, Ztschr. f. d. ges. exper. Med. **49**:71, 1926.

11. Bookman, Arthur; and Rosenthal, Julius: The Clinical Value of Intravenous Injection of Congo Red in the Diagnosis of Amyloid Disease, Am. J. M. Sc. **173**:396, 1927.

obese subjects, the correlation coefficient of the volume of the blood to the weight of the body and the surface area is essentially the same.

Data Obtained on Edema by the Dye Method.—A number of workers have studied the volume of the blood and plasma in cases of edema of different types. Keith, Rowntree and Geraghty in their original report found normal values for plasma volume in cases of edema of glomerular nephritis. Bock [12] found a normal volume of plasma according to the body weight in cases of glomerular nephritis with edema. He noted the relative constancy of the volume of the plasma during different stages of edema. Brown and Roth [13] showed that the decrease of hemoglobin and erythrocytes in chronic glomerular nephritis was due to an absolute and not to a percentage change. The volumes of blood and of plasma were similar to those observed in the usual cases of secondary anemia. Linder, Lundsgaard and Van Slyke [14] found that the reduction in concentration of the plasma proteins that is observed in certain patients with nephritis is due to an actual decrease in the amount of these substances. They found normal volume of blood even in cases of extreme edema. We have [15] reported observations in cases of edema of different types. We studied the volume of the blood and plasma in glomerular nephritis before and after the disappearance of the edema. Low values for the $\frac{\text{blood volume}}{\text{body weight}}$ with decreased cell to plasma volume ratios ("oligocythemic hypovolemia") were found during edema. The $\frac{\text{plasma volume}}{\text{body weight}}$ showed normal values. The changes following diuresis were inconstant and not marked. In three cases of nephrosis with edema, simple "normovolemia" or "oligocythemic hypervolemia" was present.

PRESENT STUDY

This study was based on twelve cases of acute and subacute glomerular nephritis and on nine cases of pure or mixed types of nephrosis, all showing marked grades of edema. The diagnosis of nephrosis was based on the presence of marked albuminuria, generalized edema, a decrease in the proteins in the blood and an increase in the values for lipoids and for the globulin in the serum. Hypertension, definite anemia and the usual cardiovascular changes observed in glomerular nephritis are lacking in the pure forms of nephrosis. The

12. Bock, A. V.: The Constancy of the Volume of Blood Plasma, Arch. Int Med. **27**:83 (Jan.) 1921.

13. Brown, G. E., and Roth, G. M.: The Anemia of Chronic Nephritis, Arch. Int. Med. **30**:817 (Dec.) 1922.

14. Linder, G. C.; Lundsgaard, C., and Van Slyke, D. D.: The Concentration of the Plasma Proteins in Nephritis, J. Exper. Med. **39**:887, 1924.

15. Brown, G. E., and Rowntree, L. G.: The Volume and Composition of the Blood and the Changes Incident to Diuresis, in Cases of Edema, Arch. Int. Med. **35**:129 (Jan.) 1925.

mixed forms as described by Volhard, with some features of glomerular nephritis, are the usual types observed. These usually progress and eventually may present the typical picture and termination of glomerular nephritis. Determinations of the volume of blood were made during the period of maximal edema and after diuresis. The treatment included the usual measures, a diet that contained little salt and fluid and the administration of massive doses of calcium and ammonium salts. During the last two years, we have employed injections of merbaphen (novasurol)

TABLE 2.—*Volume of Blood and of Plasma in Glomerular Nephritis with Edema*

					Blood			Plasma				
Case	Sex	Age	Hemoglobin, Gm. per 100 Cc.	Percentage of Cells by Hematocrit	Volume, Cc.	Cc. for Each Kg. Body Weight	Cc. for Each Square Meter Surface Area	Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Square Meter Surface Area	Grade of Edema	Remarks
5	M	22	12.8	28	4,900	89	2,850	3,530	64	2,050	3+	Subacute glomerular nephritis with anemia
6	M	21	12.9	24	4,390	66	2,500	3,330	36	1,900	3	Generalized edema, ascites
7	F	17	13.7	36	5,210	80	2,910	3,330	51	1,860	3+	Uremia, pulmonary edema
8	M	15	10.7	31	3,620	70	.....	2,500	48	.....	4	Ascites
9	M	46	12.8	27	4,740	59	2,370	3,460	43	1,730	2+	Progressive edema and anemia
10	F	25	12.6	25	3,050	58	2,130	2,280	44	1,600	3+	Ascites
11	F	16	12.7	35	3,900	59	2,050	2,540	38	1,340	3	Acute flare-up of chronic glomerular nephritis
12	M	20	14.9	31	4,540	75	2,680	3,130	52	1,850	1	Acute nephritis, pneumonia
13	M	17	6.2	11	4.050	71	2,440	3,600	63	2,150	2	Acute nephritis, mastoiditis
14	M	20	17.6	41	7,010	93	4,220	4,140	55	2,500	2	Acute nephritis, one month duration
15	M	20	9.4	28	4,580	75	2,760	3,300	54	1,930	2	Some elements of nephrosis
16	F	26	9.7	33	4,835	105	.....	3,240	70	.....	3	Subacute nephritis

Mean Values: blood volume = 74.5 ± 3 cc. for each Kg. of body weight or 2,719.5 ± 123 cc. for each square meter; plasma volume = 51.9 ± 2 cc. for each Kg. of body weight or 1,899.5 ± 63 cc. for each square meter; hemoglobin = 12.12 ± 5.1 Gm. percentage; percentage of cells by the hematocrit = 29.5 ± 1.

with or without the administration of calcium and ammonium salts in cases in which there has not been retention of nitrogen. Paracentesis was performed in several cases.

The volume of the blood was calculated on the basis of the body weight of the edema-free period, designated as the corrected body weight. The volume on the basis of surface area is also given. The surface area was calculated according to the DuBois standards and for the corrected body weight. The data on the volume in eighteen cases of secondary anemia and ten cases of pernicious anemia were used as a contrast group.

Glomerular Nephritis with Edema.—The mean volume of blood (table 2) with its probable error for the group was 74.5 ± 3 cc. for each kilogram of corrected body weight, that is, 15 cc. for each kilogram less than normal, or 2,719.5 ± 123 cc. for each square meter. The range was

from 58 to 93 cc. for each kilogram or from 2,050 to 4,220 cc. for each square meter. The mean volume of plasma was practically normal, 51.9 ± 2 cc. for each kilogram or 1,899.5 ± 63 cc. for each square meter. The range was from 36 to 64 cc. The mean percentage of cells as shown

TABLE 3.—*The Volume of Blood and Plasma in the Edema, Edema-Free and Recovery Periods in Subacute Glomerular Nephritis*

Case	Date	Hemoglobin, Gm. per 100 Cc.	Percentage of Cells by Hematocrit	Blood, Cc. for Each Kg. of Body Weight* Volume, Cc.	Uncorrected	Corrected	Plasma, Cc. for Each Kg. of Body Weight Volume, Cc.	Uncorrected	Corrected	Body Weight, Kg.	Remarks
5	12/ 3/25	12.8	28	4,900	54	73	3,530	39	53	90	Edema graded 3
	12/22/25	12.8	30	4,150	52	62	2,910	38	43	80	Edema graded 2
	1/25/26	14.3	30	4,320	72	64	3,020	50	45	60	Edema free
	11/24/26	13.8	35	5,720	86	86	3,710	56	56	67	Patient fairly well 11 months later
6	8/ 7/23	12.4	24	4,390	48	68	3,300	36	51	90	Edema graded 3
	9/11/23	12.9	29	4,100	62	62	2,930	45	45	64	Edema
10	11/15/22	12.6	25	3,060	50	61	2,280	37	46	61	Edema graded 3, anemia, ascites
	1/ 5/23	8.0	19	3,300	66	64	2,590	54	52	50	Edema free
	9/ 6/23	17.0	37	4,020	89	89	2,910	55	58	52	Apparently recovered
13	6/ 2/23	6.2	11	4,050	62	72	3,600	55	64	65	Acute nephritis, edema 3
	7/ 3/23	8.1	20	3,300	60	60	2,640	47	47	56	Edema graded 1
14	2/20/23	17.6	41	7,010	84	91	4,140	49	55	83	Acute nephritis, edema 3
	3/ 1/23	17.3	42	6,900	97	90	4,000	56	54	71	Edema free
	5/16/23	17.0	40	6,860	92	90	4,120	55	55	75	Edema free
	12/12/23	18.5	45	7,190	96	95	3,950	52	52	75	Good recovery, no edema
16	4/ 6/27	9.7	33	4,835	78	105	3,240	52	70	62	Edema graded 3
	5/ 3/27	11.0	20	4,250	..	91	3,390	..	73	46	Weight loss, both fluid and body protein

* Body weight in the postedema period = corrected body weight; body weight in the edema period = uncorrected body weight.

TABLE 4.—*Summary of Changes in the Volume of the Blood and of Plasma Occurring During Diuresis in Glomerular Nephritis*

Case	Weight Loss, Kg.	Percentage Change of Cells by Hematocrit	Blood Volume Increase, Cc.	Blood Volume Decrease, Cc.	Plasma Volume Increase, Cc.	Plasma Volume Decrease, Cc.	Duration of Time for Diuresis, Days
5	30	+2	...	580	...	500	63
6	27	+5	...	290	...	370	34
7	2.5	−9	...	940	...	170	14
9	8.5	−13	...	2,060	...	880	83
10	14	−6	150	...	310	...	50
13	9	+9	...	750	...	960	31
14	10	...	...	100	...	150	11
16	16	−13	...	585	155	...	27

by the hematocrit was 29.5 ± 1 (the normal value is 42 per cent) and the hemoglobin in grams per hundred cubic centimeters of blood was 12.1 ± 5.1 as contrasted with the normal value, 15.6 per cent.[16] The mean values in this study corroborate our original claim that "oligocythemic hypovolemia" characterizes glomerular nephritis.

16. Haden's value for both sexes.

Changes During Diuresis in Chronic Glomerular Nephritis.—The variations in the volume of the blood and plasma during diuresis are shown in table 3. A summary of the changes occurring in eight cases with two or more determinations of volume during the period of treatment are shown in table 4. There is a fairly constant directional change in the volume of blood during the period of diuresis, as seven of the eight cases showed a decrease in the volume of blood. In case 5 there was a loss of 500 cc. in the volume of the blood, which was entirely due to a loss in plasma; in case 6 there was a decrease of 370 cc. of plasma; in case 7, there was a large loss in the volume of blood, which was

TABLE 5.—*The Volume of the Blood and of Plasma in Nephrosis, Edema Stage*

					Blood			Plasma				
Case	Sex	Age	Hemoglobin, Gm. per 100 Cc.	Percentage of Cells by Hematocrit	Volume, Cc.	Cc. for Each Kg. Body Weight	Cc. for Each Square Meter Surface Area	Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Square Meter Surface Area	Edema, Grade 1-4	Remarks
1	M	23	15.9	50	5,750	84	.....	2,875	42	.....	3+	Probably a case of pure nephrosis
4	F	25	11.6	39	4,665	103	.....	2,845	64	.....	3+	Nephrosis with some features of glomerular involvement
9	M	46	18.6	38	6,830	81	3,500	4,240	50	2,170	4	Nephrosis picture, at this stage ascites 2
17	M	37	19.6	45	6,080	89	3,630	3,670	49	2,000	2	Edema 2, ascites 1, mixed nephrosis
18	M	33	19.8	44	5,100	102	.....	2,860	57	.....	2	Emaciated
19	M	25	17.0	39	5,370	93	3,210	3,270	56	1,950	3	Generalized edema
20	M	32	12.3	30	5,780	101	3,450	4,050	71	2,420	2-3	Mixed lesions, glomerular nephritis
21	M	31	12.5	33	4,850	99	3,070	3,240	66	2,050	1+	Mild nephrosis
22	M	19	14.2	24	6,010	105	3,800	4,570	80	2,710	2+	Nephrosis and Pott's disease

Mean Values: blood volume = 94.8 ± 2 cc. for each Kg. or 3,449.5 ± 60 cc. for each square meter; plasma volume = 60.0 ± 3 cc. for each Kg. or 2,123.5 ± 81 cc. for each square meter; hemoglobin = 15.7 ± 7.2 Gm. percentage; percentage of cells by the hematocrit = 37.5 ± 2.

almost entirely due to cells; in case 9, there was a huge decrease in the blood mass, two thirds of which was cells; in case 10, there were not any significant changes; in case thirteen, there was a loss of 960 cc. of plasma. The changes were not significant in case 14. In case 16, the volume of blood decreased 580 cc., which was largely a decrease in cells. The loss in weight due to diuresis varied in these subjects from 2.5 to 30 Kg. The duration of treatment varied from six to ninety days.

Nephrosis.—On the basis of the corrected body weight, the mean volume of blood during the stage of edema in nine cases of nephrosis was 94.8 ± 2 cc. for each kilogram or 5 cc. more than the normal mean, or 3,449 ± 60 cc. for each square meter of surface area. These figures for the mean value are still within the normal upper range. The variation in the group was from 81 to 105 cc. for each kilogram or 3,070 to

3,800 cc. according to area. The mean volume of plasma was 60 ± 3 cc. or 10 cc. (20 per cent) more than the normal, and 2,123.5 ± 81 cc. according to weight and surface area, respectively, or 150 cc. more than normal. The variations were from 49 to 80 cc. for weight and 1,950 to 2,710 cc. for surface area. The mean hemoglobin content in grams per hundred cubic centimeters of blood was 15.7 ± 7.2 and the mean percentage of cells as shown by the hematocrit was 37.5 ± 2. A mild grade of anemia was present in four cases.

A study of these mean values indicates that there is a moderate increase in the mean total volume of blood and a definite increase in the mean volume of plasma as compared to the normal. This would be interpreted as "oligocythemic hypervolemia." Although the mean values are high, five of the nine cases showed values that were strictly normal, "normovolemia simplex." It would appear that in cases of nephrosis with edema, the volume of blood and of plasma tends to become

TABLE 6.—*Changes in the Volume of Blood and of Plasma with Diuresis in Cases of Nephrosis*

Case	Weight Loss, Kg.	Percentage of Cells by the Hematocrit, Changes	Blood Decrease, Cc.	Plasma		Duration of Dehydration Period, Days
				Increase, Cc.	Decrease, Cc.	
1	8	−7	...	395	...	11
4	15	−7	105	255	...	16
9	4	−3	300	...	...	30
17	10	−1	...	...	...	22
19	15	−2	...	...	...	24
22	9	+1	600	...	400	13

increased. It is also interesting that in the four cases with the largest volume of plasma some evidence of anemia was shown by the decreased values for hemoglobin, and percentage of cells by the hematocrit. It is evident, therefore, that nephrosis with edema may be associated with normal or increased volume of blood and of plasma, "simple normovolemia" or "oligocythemic hypervolemia."

Table 6 gives the summarized data of the changes that occur in blood and plasma with diuresis in nephrosis. In only one case, case 22, were significant changes observed. A loss of 600 cc. of blood occurred, 400 cc. of which was due to a decrease in the plasma. In case 1, there was a slight loss in plasma. Control of the edema, therefore, does not appear to influence the volume of blood to any appreciable degree.

Changes Observed in Nephrosis When the Signs and Symptoms of Glomerular Nephritis Subsequently Develop.—Data concerning the volume of blood in case 9, which when first observed presentetd a classic example of nephrosis, are given in table 7. The blood pressure was normal and the blood cholesterol high, while the protein in the serum was reduced. The volume of the blood was 81 cc. for each kilogram of

normal weight;[17] the volume of plasma was 53 cc. This was during the period of maximal general anasarca and ascites. The hemoglobin in grams per hundred cubic centimeters was 18.6, and there was 38 per cent of cells, as ascertained by the hematocrit. During a period of two months, the edema fluctuated; various forms of treatment were used: desiccated thyroid, massive doses of calcium and later abdominal paracentesis. The hemoglobin showed a gradual reduction comparable to the reduction in the volume of cells. The total volume of blood decreased to 59 cc. for each kilogram, and the volume of plasma decreased to 42 cc. for each kilogram. At the final examination, retention of urea had developed, the blood pressure had increased, and glomerular nephritis was evident. The

TABLE 7.—*Nephrosis: Subsequent Development of Subacute Glomerular Nephritis with Anemia*

				Blood		Plasma			
Case	Date	Hemoglobin, Gm. per 100 Cc.	Percentage Hemoglobin, by Hematocrit	Volume, Cc.	Cc. for Each Kg. Body Weight, Corrected*	Volume, Cc.	Cc. for Each Kg. Body Weight, Corrected*	Body Weight, Kg.	Comment
9	10/ 7/22	18.6	38	6,830	81	4,240	53	94	Marked edema, ascites
	10/17/22	17.0	43	7,340	91	4,190	52	90	Some dye in urine
	10/21/22	17.0	35	6,220	78	4,040	51	90	
	11/ 7/22	16.8	40	5,710	71	3,460	43	90	
	11/17/22	13.3	35	6,510	81	4,240	53	87	Paracentesis abdominis
	11/29/22	13.1	37	6,720	84	4,240	53	86	
	12/ 7/22	13.8	28	4,910	63	3,830	48	90	
	12/13/22	12.8	27	4,740	59	3,460	43	89	
	12/23/22	10.9	28	5,210	65	3,750	47	90	
	12/30/22	9.6	29	4,740	59	3,360	42	88	Edema 2, ascites 1

* Weight corrected on the basis of his normal weight, 80 Kg.

volume of blood and of plasma had decreased materially, but it did not show any fluctuations that were related to the fluctuation in the degree of edema, but preceded paripassu with the progressing anemia.

Data on Volume of Blood in Glomerular Nephritis.—There is no evidence that dilution of the blood occurs in subjects with the edema that accompanies glomerular nephritis. When calculated on the basis of the corrected body weight, a normal or a decreased volume ("normovolemia or hypovolemia") is the rule. On the basis of the changes in the blood, cases of glomerular nephritis can be divided into two groups: those in which there is anemia and those in which anemia does not occur. The latter group consists largely of cases of the mild and of the more acute forms of the disease. In the subacute or chronic stages anemia is almost uniformly present in some degree. The pallor of these subjects, the decreased specific gravity of the blood and the decrease in erythrocytes,

17. This patient never became free from edema, and his usual normal weight was used as the corrected body weight.

in the presence of edema, seem at first sight evidence of blood dilution. These changes, however, are similar to those found in simple chronic anemia without edema. The anemia in nephritis is due to an absolute decrease in erythrocytes, since the volume of plasma is not increased to produce dilution or an apparent anemia. The lowered specific gravity of the plasma and decreased percentage of protein have been shown to

TABLE 8.—*Mean Values with Probable Error*

Group	Case	Hemoglobin, Gm. per 100 Cc.	Percentage of Cells by Hematocrit	Volume of Blood: Cc. for Each Kg. of Weight	Volume of Blood: Cc. for Each Square Meter of Area	Range	Cc. for Each Kg. of Weight	Cc. for Each Square Meter of Area	Range
Glomerular nephritis with edema	12	12.1 ± 5.1	29.5 ± 1	74.5 ± 3	2719.5 ± 128	58- 93	51.9 ± 2	1889.5 ± 68	30-64
Nephrosis with edema.....	9	15.7 ± 7.2	37.5 ± 2	94.8 ± 2	3449.5 ± 60	81-105	60.0 ± 3	2123.5 ± 81	49-80
Chronic secondary anemia..	18	11.45 ± 4.3	30.5 ± 9.6	82.8 ± 2.9	2705.5 ± 94.2	50-110	52.7 ± 1.9	1990.5 ± 95.3	34-76
Pernicious anemia.....	10	11.0 ± 5.2	22.6 ± 14.4	77.0 ± 1.7	2771.7 ± 42	65- 90	60.2 ± 1.1	2194 ± 47.5	50-68
Normal*	56	17.8 ± 0.2	42.1 ± 2	89.1 ± 0.6	3383 ± 33	70-100	50 ± 0.5	1973 ± 20	40-60

* This group is not a representative normal group but is composed of a selected group of normal adults, most of whom were males.

TABLE 9.—*Blood and Plasma Volume in Polycythemia Vera Under Treatment with Phenylhydrazine Hydrochloride*

Case	Date	Hemoglobin, Gm. per 100 Cc.	Hematocrit, Cells, per Cent	Volume of Blood: Total, Cc.	Volume of Blood: Cc. for Each Kg.	Volume of Plasma: Total, Cc.	Volume of Plasma: Cc. for Each Kg.
23	12/15/24	22.5	67	11,000	183	3,630	60
	12/28/24	21.4	68	7,973	142	2,950	52
	1/ 7/25	18.1	63	10,800	180	4,000	70
	1/14/25	19.9	65	9,900	173	3,460	60
	2/ 4/25	16	56	8,520	157	3,750	69
	2/11/25	12.4	40	6,510	116	3,910	70
	2/16/25	11.5	39	5,800	103	3,530	63
24	.....	26	75	14,700	180	3,675	46
	12/23/25	....	43	6,940	90	3,955	52
	1/ 4/26	....	24	5,660	75	4,290	57
25	11/14/25	4.5	60	8,580	136	3,430	54
	12/ 7/25	12.8	32	4,514	71	3,076	48
26	8/10/25	24	50	8,607	136	3,529	55
	8/17/25	....	37	5,962	93	5,750	58
	8/28/25	5.7	..	5,500	87	4,675	72

be due to an absolute loss of albumin in the blood. Our data show that the mean volume of blood in glomerular nephritis, when corrected for the edema-free body weight, is less than normal, while the mean volume of plasma is quite normal ("oligocythemic hypovolemia"). The decrease in the total volume depends on the decreased volume of cells and indicates true anemia.

Plasma Cell Relationships in Anemia.—As is known, in certain forms of anemia a replacement, compensatory or restoration process occurs to maintain an adequate volume of blood. Plasma enters the blood quickly following bleeding, while replacement of cells occurs more slowly. In the chronic types of anemia, in which cells are reduced without loss of plasma, the mechanism is variable. Studies of the volumes of blood and of plasma in the simple and primary types of anemia show definite differences in these two forms (table 8). It will be observed from the data that the mean volume of plasma in eighteen cases of chronic secondary anemia is 56.7 ± 1.9 cc. for each kilogram of body weight. This is above the normal value, while the relative absolute volume of blood is moderately reduced, 82.8 ± 2.9, owing to the diminished volume of cells. It is apparent that replacement of cells by plasma is moderate. It was found that in ten subjects with pernicious anemia, the mean volume of plasma was 60 cc. for each kilogram of body weight. The total volume of blood and of cells was lower than in secondary anemia, since the degree of anemia was more marked. The higher values for the volume of plasma would indicate that in pernicious anemia there was a partial replacement of cells by plasma. Similar high volumes of plasma were found by Keith [18] in twelve cases of pernicious anemia. In one of the cases with a decrease in the hemoglobin of 20 per cent and in the percentage of cells of 40 per cent as determined by the hematocrit, the volume of plasma increased 9 cc. for each kilogram of body weight, or approximately 15 per cent over the former volume of plasma. In one case in which the hemoglobin and erythrocytes were increasing, there was a reduction in the relative plasma to offset the increased volume of cells. This difference of response of the replacement mechanism in different forms of anemia is of interest and requires further investigation. We have obtained further information concerning the response of the plasma to loss of cells in cases of polycythemia vera in which the patient is treated with phenylhydrazine. With this form of treatment there is rapid destruction of erythrocytes within a few days. The volumes of the blood and of the plasma during the period of destruction of the blood are shown in table 9. Within fifty days, there was a decrease of 6.5 Gm. of hemoglobin for each 100 cc. of blood in case 23 and a decrease of 11 in the percentage of cells as shown by the hematocrit, with an increase of 9 cc. of plasma for each kilogram of body weight, or approximately 15 per cent. With further reduction in the volume of cells and of hemoglobin, there was no further increase in the volume of the plasma. Similar increases in the volume of the plasma were observed in cases 24 and 26.

18. Keith, N. M.: Total Circulating Volume of Blood and Plasma in Chronic Anemia and Leukemia, Am. J. M. Sc. **165**:174, 1923.

Comparing the data concerning the volume of blood in the cases of glomerular nephritis accompanied by edema and anemia with these in cases of secondary anemia, a definite dissimilarity is apparent (chart 2). The mean volume of plasma in the cases of glomerular nephritis is lower than in secondary anemia, and the grade of anemia is comparable for both groups. The replacement of cells by plasma does not occur or at least is not maintained and diuresis per se produces no significant variations in the volume of blood and plasma in cases of glomerular nephritis.

The changes occurring in the volume of blood during diuresis in glomerular nephritis are largely those due to further decrease in the

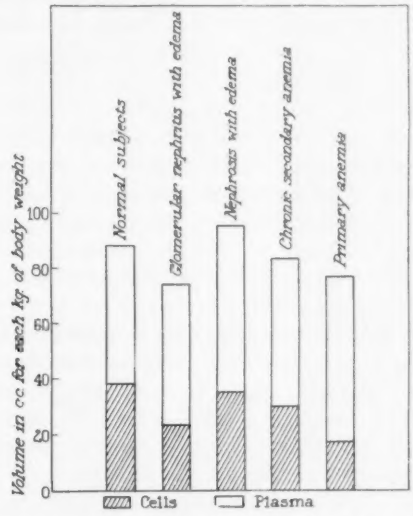

Chart 2.—Mean volumes of the blood, according to body weight, in glomerular nephritis, nephrosis and chronic anemia. The diagonal lines indicate the blood cells and the blank spaces the blood plasma.

volume of cells, indicating that progressive anemia is developing during the period of diuresis. This is not due to dilution, since the volume of plasma maintains a fairly constant level while the volume of cells is progressively diminishing. Restoration of the volume of blood by plasma does not occur. The proof of this is given in case 9 in which the studies of volume were carried out during the period of the development of the anemia or during the transition stage from what was apparently a case of nephrosis to true glomerular nephritis. The constancy of the relation of the volume of plasma to body weight during the period of developing anemia and fluctuating edema is quite evident. The relative volume of

plasma remained fairly constant until the anemia was definitely present or until the hemoglobin had become reduced to 12.8 Gm. per hundred cubic centimeters. With further reduction of the hemoglobin to 9.6 Gm. per 100 cubic centimeters, there was a decrease in the volume of the plasma of 6 cc. for each kilogram of body weight. This variation in the volume of plasma could not be correlated to fluctuations in the amount of edema.

Data on the Volume of the Blood in Nephrosis.—Anemia is not marked or constant in nephrosis. Elwyn stated that "moderate anemia is present averaging 4,000,000 erythrocytes for each centimeter and that with the disappearance of edema temporary blood dilution with an increased anemia occurs." Our data show that in five of the nine cases the hemoglobin values and those obtained by the hematocrit were normal; in the remaining four cases, there was a mild degree of anemia. The mean hemoglobin in grams per hundred cubic centimeters was 15.7 ± 7.2, and the mean percentage of cells as ascertained by the hematocrit was 37.5 ± 2. In the cases without anemia the average volume of blood was 88 cc. for each kilogram, and the average volume of plasma was 51 cc. for each kilogram. These volumes are quite normal. In the four cases of mild anemia, the average volume of blood was 102 cc. for each kilogram of body weight, and the amount of plasma was 70 cc. for each kilogram. Taking the group as a whole, the mean volume of blood in cases of nephrosis is about 5 cc. higher than the normal mean and 20 cc. higher than the mean in glomerular nephritis (table 8, chart 2). When the mean values of the entire group are compared with those in non-nephritic chronic secondary anemia, the mean volume of blood and plasma is 12 cc. and 3.3 cc., respectively, greater in the cases of nephrosis; as compared to primary or pernicious anemia, the mean volume of blood is 17 cc. higher in the group of cases of nephrosis, while the volume of plasma is identical in the two groups.

If the cases of nephrosis with anemia are compared with those of chronic secondary anemia and pernicious anemia, it is apparent that both the volume of blood and the volume of plasma are definitely greater, while the degree of anemia is less in the cases of nephrosis.

These data are quite different from those in glomerular nephritis; the volume of cells is only slightly decreased in the cases of nephrosis, while in glomerular nephrosis it is markedly lowered, and the mean volume of plasma is about 10 cc. higher in nephrosis than in glomerular nephritis. The explanation for this dissimilarity is not entirely clear. One would be tempted to assume that the relatively high volume of plasma in nephrosis represents an example of blood dilution, and that the increased volume of plasma, which is about 20 per cent, would be sufficient to produce apparent or dilution anemia. An argument against this is the slight or negligible changes occurring in the volume of blood and of plasma with diuresis. In only one case was definite variation

observed, a decrease of 600 cc. of whole blood, of which two-thirds was due to decrease in the plasma. In the other cases, the changes were slight and did not show a constant directional tendency.

It could also be assumed that when true mild anemia is present in some cases of nephrosis that the replacement of cells by plasma is more than adequate. The objection to this hypothesis rests on the fact that our data show the mean volume of blood and of plasma in cases of nephrosis with anemia to be 13 cc. and 20 cc. higher, respectively, than the normal mean. Restoration of blood mass by plasma in response to loss of cells would then be excessive, a conception that is difficult to explain. The loss of dye in the urine in cases of nephrosis, if sufficient to produce an abnormal or too rapid disappearance of the dye in the blood serum, would give an abnormally high or false volume of plasma. We studied the rates of disappearance of the dye in the blood serum in four cases of nephrosis in which dye was present in the urine within ten minutes after its injection. Table 1 shows that, as compared with the normal, there was a greater decrease in the percentage of concentration of the dye in the two to six minute interval as shown by the volume of plasma. This difference, 1.5 per cent, appears to us too small to explain fully the relatively high values of the volume of plasma in the cases of nephrosis. In order to settle the question definitely, it would be necessary to study the volumes before and during the development of the disease.

These studies on the volumes of the blood and plasma in cases of glomerular nephritis and nephrosis and primary and secondary anemia suggest the following hypothesis: The changes occurring in the plasma volume are in large part related to loss of cells. The decrease in cell volume is replaced by plasma. This replacement is usually not complete and varies in different forms of anemia. In chronic secondary anemia replacement is partially complete, but not as marked as in the primary forms and in anemia associated with splenomegaly. In glomerular nephritis with edema and a secondary type of anemia, replacement by plasma occurs to a slight extent or not at all. Edema may be an essential factor in withholding plasma from the blood. In nephrosis without anemia these factors apparently do not obtain, and the blood and plasma volumes are normal. When anemia occurs, there is an increase of plasma. As edema is common to both groups, the anemia appears to be a more critical factor than edema in determining the status of the plasma volumes.

SUMMARY

A low or low normal volume of blood is found in cases of glomerular nephritis with edema. The reduction in the volume of blood is due to a diminished volume of cells. The mean volume of plasma is normal; this indicates actual anemia. According to the new terminology, the volume

state is "oligocythemic normovolemia" or "oligocythemic hypovolemia." During diuresis, the significant changes in the blood volume and of plasma are those related to further reduction in the volume of cells, that is, to the progression of the anemia. In chronic nephritis with edema a form of the chronic secondary anemia due to deficient erythrogenesis is present and replacement of cells by plasma does not occur, or, at least, is not adequately maintained.

In cases of nephrosis with edema, approximately 50 per cent do not show anemia; the remainder show mild grades of anemia. In the non-anemic group, strictly normal values for the volume of blood and of plasma are obtained ("simple normovolemia"); in cases with diminished hemoglobin and cell values, the volume of blood and plasma are definitely increased, "oligocythemic hypervolemia." The increase in the blood volume and of plasma is excessive. An explanation of this increase of blood volume and plasma by restoration of plasma is not at hand; there is no good evidence to indicate that in these cases a dilution phenomenon occurs, and diuresis does not produce any changes in the volume of blood and of plasma, which admittedly is evidence against the dilution theory. Abnormal loss of dye in the urine may account in part, but not wholly, for the increase in the volume of plasma.

These values for the volume of blood and of plasma in cases of glomerular nephritis and nephrosis accompanied by edema are comparable to those reported in our previous study of a smaller group of cases.

MUMPS POLYNEURITIS

QUADRIPLEGIA WITH BILATERAL FACIAL PARALYSIS *

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The neurologic complications occurring in mumps have frequently been observed and recorded. They may be classified into the following types: (1) meningitis,[1] (2) encephalitis [2] and (3) neuritis: (*a*) second, sixth, seventh, eighth, eleventh and twelfth cranial nerves,[3] (*b*) diffuse polyneuritis and (c) localized neuritis. An excellent review of the literature up to 1898 was made by Gallavardin,[4] and another review to 1915 was made by Feiling.[5]

We record a unique case of polyneuritis in which all extremities of the patient were affected with bilateral facial involvement complicating epidemic parotitis. We have been able to find only four cases of diffuse polyneuritis in the literature—all were described by the French.

REVIEW OF THE LITERATURE

Joffroy [6] was the first to call attention to this syndrome. He reported the case of a child, aged 4½ years, who, during convalescence, developed a quadriplegia three weeks after the onset of epidemic parotitis. Neurologic examination revealed a loss of all the deep and superficial reflexes, generalized superficial hypesthesia and an abolition of faradic contractility. The cranial nerves were not involved. The child began to improve about the third month, and by the fourth month almost all motor power had returned. Eleven months later, the child was found to have made a complete recovery.

Revilliod [7] recorded the second case which was that of a child, aged 7 years, who contracted epidemic parotitis. One week after the onset of

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* From the Department of Medicine and the Harry Caplin Research Laboratory, Jewish Hospital.

1. Acker, G. N.: Parotitis Complicated with Meningitis, Am. J. Dis. Child. **6**:399 (Dec.) 1913.
2. Haden, R. L.: The Cerebral Complications of Mumps, Arch. Int. Med. **23**:737 (June) 1919.
3. Lannois: Lyon méd. **93**:469, 1900. Roger and Magarot: Rev. méd. 1909, p. 826.
4. Gallavardin, M. L.: Gaz. d. hóp. **71**:1329, 1898.
5. Feiling, A.: Quart. J. Med. **8**:257, 1915.
6. Joffroy, A: Progrès méd., 1886, p. 1009.
7. Revilliod, L.: Rev. méd. de la Suisse romande **16**:752, 1896.

the mumps, the child developed a marked weakness in the legs and disturbance in deglutition. Examination revealed a quadriplegia with a loss in the superficial and deep reflexes, bilateral sixth nerve paralysis and left facial and right hypoglossal weakness. There were no sensory or trophic disorders, and the special senses were intact. One week later, the child was able to stand and by the end of two months, he had made a complete recovery.

The third case was reported by Gallavardin,[4] that of a woman, aged 31, who developed a flaccid paralysis of all the limbs two weeks after the onset of the mumps. There was a loss of all the reflexes and deep muscle sense and a diminution in response to faradic stimulation. She made slow progressive improvement.

Pitres and Marchand [8] record a case of quadriplegic polyneuritic paralysis occurring in a young soldier during convalescence from mumps. The paralysis appeared two weeks after the onset of mumps. There was a loss of all the reflexes and an abolition of deep muscle and stereognostic sense; the cranial nerves were not involved. The patient was still slightly incapacitated at the end of a year.

Other cases of hemiplegia and diplegia of either the upper or lower extremities of peripheral origin have also been reported.[9]

REPORT OF CASE

History.—A young man, aged 29, contracted a mild attack of epidemic parotitis which subsided in five days. One week after the onset, he developed a left orchitis accompanied by chills and a temperature of 104 F. The orchitis subsided in one week, with resulting atrophy of the testicle. On May 28th, three weeks after the onset of his present illness, he complained of weakness in the lower extremities, and found that he was unable to stand. He became progressively worse, and within forty-eight hours was unable to sit or roll over in bed. He also complained of some disturbance in swallowing food.

Examination.—Physical examination revealed a well developed and well nourished young man who did not appear acutely ill. He lay flat on his back, unable to move his head or his extremities. His neck was rigid, his head in slight opisthotonus. He showed a complete bilateral upper and lower facial paralysis. Difficulty in swallowing was really difficulty in ingesting food owing to his facial paralysis. All the other cranial nerves were uninvolved. There was a complete paretic quadriplegia, with greater involvement of the extensor than the flexor group of muscles, and a marked bilateral Kernig sign. He showed a loss of all the deep reflexes, nor could any superficial reflexes be elicited. All plantar reflex phenomena were absent. The sensory changes occurred twenty-four hours later, and consisted of paresthesia of the feet, such as tingling and burning sensations, hypesthesia of the arms and legs, hyperesthesia of the hands and feet and loss of joint and vibratory sense in all extremities.

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8. Pitres, A. and Marchand, L.: Progrès méd. **50**:397, 1922.

9. Sainton and Huriez: Bull. et mém. Soc. méd. d. hôp de Paris **39**:809, 1915; Loire méd., 1891.

A lumbar puncture done on the fourth day of his neurologic complication showed clear spinal fluid under pressure, containing 18 lymphocytes per cubic millimeter. The fluid on analysis showed: a 2 mm. albumin ring, globulin four plus, 44 mg. of sugar per hundred cubic centimeters. The Wassermann reaction was negative, the smear was negative for *Bacillus tuberculosis* or other organisms, the culture was sterile, and the colloidal gold curve was 00000000. A lumbar puncture the following day showed clear fluid under normal pressure, containing only 3 lymphocytes per cubic millimeter. The patient's urine was normal except for a faint trace of albumin.

The blood count showed: hemoglobin, 85 per cent; red blood cells, 5,300,000; white blood cells, 13,000; polymorphonuclear leukocytes, 56 per cent; lymphocytes, 40 per cent. The blood pressure was 142 systolic and 74 diastolic.

Diagnosis.—In view of the fact that there was a specific etiologic factor present to account for this symptom complex, a provisional diagnosis was made of diffuse quadriplegic polyneuritis with a bilateral peripheral facial paralysis and meningitis, arising from an epidemic parotitis.

Course of Illness.—June 6, 1927 (one week later).—The patient began to show evidence of a regression of his lesion, some muscular power was returning in all extremities, and the plantar flexion phenomenon of the right foot was present.

June 10: Voluntary movement of right facial group muscles was returning. Hypesthesia of the legs was clearing up.

June 13: The patient started to receive strychnine sulphate 1/30 grain (0.002 Gm.) three times a day.

June 14: It was noted that the patient had made rapid improvement during the preceeding twenty-four hours; the motor signs improved faster than the sensory; the abdominal reflexes were present but exhaustible.

June 18: The patient was able to raise the arms above the head. The thighs and legs could be well flexed.

June 20: The patient was discharged from the hospital in the following condition: no rigidity of the neck; slight bilateral Kernig sign present; condition of cranial nerves: could wrinkle forehead; closed eyelids poorly; smiled slightly; barely able to show his teeth; fundi normal; hearing normal; taste and smell normal; hypesthesia of anterior portion of tongue gone; movements of tongue normal; eleventh nerve normal; pharyngeal reflex present; spinal motor reactions: had good grip; flexors of arm good, right better than left; muscles of legs markedly improved; quadriceps contraction good; able to sit up with slight support but required assistance to sitting position; no drop foot; sensory reactions: superficial sense normal; slight astereognosis and ataxia of upper extremities; deep joint sense in hands and feet absent; deep muscle and pain sense present; reflexes: abdominal, present; right cremasteric present, left not elicited; plantar flexion phenomenon of foot elicited on both sides; deep reflexes absent; visceral phenomena normal.

The patient had an atrophy of the left testicle. He was afebrile during the entire course of his neurologic disorder.

The patient was again seen on June 24, 1927 (four weeks after the onset of the paralysis). He was then able to stand with some assistance. Quadriceps extension could be maintained for thirty seconds. Right facial power was rapidly returning to normal. Deep reflexes and deep joint sense were still absent.

June 29th: The patient was able to sit up voluntarily without support. The upper extremities possessed practically normal power. The patient was able to get out of bed and stood and took a few steps with some assistance. The quadriceps extension could be maintained for one and one-half minutes. The

left joint sense in the foot had returned although the right was still absent. The joint sense in the hands was normal. All deep reflexes were absent, but all superficial reflexes were present. The power of facial movement was good, but the movement of the lower part was better than that of the upper part.

The patient was seen again on September 11. He did not exhibit any residual signs of his previous illness. All sensory, motor and reflex phenomena were normal and the patient was discharged cured.

COMMENT

All of the cases of polyneuritis reported presented the quadriplegic manifestations, but they varied in the nature of cerebral nerve involvement. These patients variously had an involvement of the second, third, sixth, seventh, eighth, ninth, eleventh and twelfth nerves. Our patient had bilateral involvement of the seventh nerve. In all of the cases reported, the motor phenomena of the patient predominated, with the sensory symptoms and signs playing a minor part. This type of polyneuritis is usually of infectious origin, and the picture closely resembles that occurring as a complication of diphtheria, influenza, typhoid fever, measles, scarlet fever, whooping cough, gonorrhea and syphilis. Toxic polyneuritis, resulting from alcohol, lead, arsenic, coal tars, mercury and other metals, also resembles this picture.[10]

The common characteristics of all of the patients with parotitic quadriplegia were flaccid paralysis of all the extremities, loss of both deep and superficial reflexes, slight or no superficial sensory disorders and a disturbance of the deep senses such as the joint and vibratory senses.

None of the cases were fatal. All of the patients recovered completely, although the duration of the illness varied from one month to one year.

The meningitis, however, which occurs with mumps is a much more frequent phenomenon. Acker [1] has collected 150 cases from the literature. Wollstein [11] states that meningitis or meningo-encephalitis occurs in 23 per cent of the cases of epidemic mumps. Gordon [12] reported four fatal cases of mumps meningitis, and at autopsy demonstrated a lymphocytic infiltration of the pia-arachnoid with flattening of the sulci as evidence of increased intracranial pressure. The spinal fluid in all cases of meningitis has always been clear and under pressure, and has contained a small number of lymphocytes (from 15 to 200) and a large amount of globulin.

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10. Pollock, L. J., and Cecil, R. L.: Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1927, p. 1334.

11. Wollstein, M. (footnote 10, p. 288).

12. Gordon, M. H.: Lancet **2**:275, 1913.

The question arises as to the exact localization of this lesion. With the absence of abdominal reflexes, the presence of meningeal signs, the few sensory manifestations and the predominatingly motor phenomena, one wonders whether in addition to the polyneuritis the patient did not have some involvement of the spinal cord. The loss of abdominal reflexes without a break in the peripheral portion of the arc, either motor or sensory, makes one suspicious that a central lesion was present. This case seems to confirm the growing concept among neuropathologists that in all cases of polyneuritis there are some minor changes in the cord.

SUMMARY

A unique case of polyneuritic quadriplegia and bilateral facial paralysis and meningitis complicating epidemic parotitis is reported.

EFFECT OF IODINE IN TOXIC ADENOMA*

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In recent years there has developed a general belief that so-called adenomatous goiter with hyperthroidism (toxic adenoma) and exophthalmic goiter are two separate diseases. Still more recently, this belief has been emphasized by the common acceptance of the view that iodine, though beneficial under certain conditions in exophthalmic goiter, is harmful to and contraindicated in cases of toxic adenoma. Such a difference in response to iodine might well be expected to occur were it true that a fundamental difference exists between these two types of thyrotoxicosis. However, conclusive evidence of such a difference has not been presented, and it seemed that further evidence concerning the nature of toxic adenoma would be obtained by a trial of the effect of iodine in such cases. Such a study could be expected to furnish further evidence of the relation existing between exophthalmic goiter and toxic adenoma. In 1924, we therefore began a study of the effect of iodine in cases of toxic adenoma.

METHODS

Unselected cases of toxic adenoma, in which treatment with iodine had not previously been used, were studied. The differential diagnosis in these cases was based on the generally accepted criteria for the diagnosis of toxic adenoma, namely, a characteristic history, the presence of a nodular goiter, absence of exophthalmos and absence of thrill and bruit over the thyroid gland. The average age of the patients in our series was 49 years, the average duration of symptoms was 2.8 years. Symptoms referable to the heart were a prominent feature in many of the cases. The pathologic observations were those of toxic adenoma in twenty-one of the twenty-five cases in which the examination was made. In the other four cases, the presence of additional changes was at best questionable. The clinical material was obtained from a region of endemic goiter where such forms of the disease are common, and the diagnoses represent the combined opinion of several experienced observers. Special care was taken to exclude the so-called mixed forms of the disease, and a large number of such cases were discarded in this study.

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* Read in abstract at the meeting of the American Society for Clinical Investigation, Atlantic City, May 2, 1927.

The plan of study called for a preliminary period of about ten days of rest in bed and ordinary medical treatment in the hospital for the purpose of diagnosis and stabilization. Iodine was then administered, nearly always in the form of a compound solution of iodine, 5 minims (0.3 cc.), three times daily, and the effect noted. As a control, unselected cases of exophthalmic goiter in which the patients were similarly treated with iodine and a few cases of toxic adenoma in which the patients were not treated with iodine were observed.

RESULTS

Seventy-eight cases of toxic adenoma were available for study, and these patients were treated with iodine. For various reasons, chiefly social and economic, the complete plan of study could not be carried out in a considerable number of the cases, but fairly complete data was obtained in thirty of the seventy-eight. Less complete data was obtained

TABLE 1.—*Percentage of Reduction of Basal Metabolic Rate to Normal in Thirty Unselected Cases of Toxic Adenoma in Which the Patients Were Treated With Iodine*

Percentage of Reduction of Basal Metabolic Rate to Normal (+10)	Number of Cases
Less than 25	6
25 to 49	9
50 to 74	8
75 to 100	7

in the remainder, and while these cases have not been used directly in this study, they offer important supplementary evidence in support of the observations obtained in the thirty cases more completely studied.

Twenty-four of the thirty pateints, or 80 per cent, showed a favorable response to the iodine similar to that observed in unselected cases of exophthalmic goiter under similar conditions. In six cases, there was little or no response. Particularly important is the fact that evidence of an unfavorable effect of the iodine was obtained only when the administration of iodine was discontinued or unduly prolonged. In such instances, to be discussed later, a relapse occurred, as is seen in exophthalmic goiter under similar circumstances.

In charts 1, 2 and 3 are shown the curves of the basal metabolic rates in the twenty-four cases in which the patients' response to iodine was favorable. In table 1, the thirty cases are grouped according to the percentage of reduction of the basal metabolism to normal; for this purpose we used the last basal metabolic rate before the administration of iodine was begun [1] and the minimum rate after iodine (before opera-

1. When determinations of the basal metabolic rate were made on the day on which the administration of iodine was started or on the following day, they have been considered as the "pre-iodine" rate in this connection.

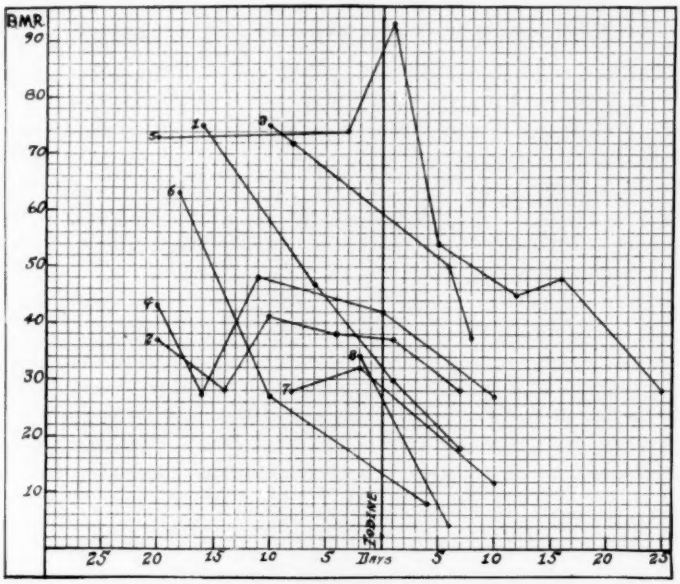

Chart 1.—Curves of basal metabolic rate in cases of toxic adenoma, 1 to 8 inclusive, in which the patients were treated with iodine.

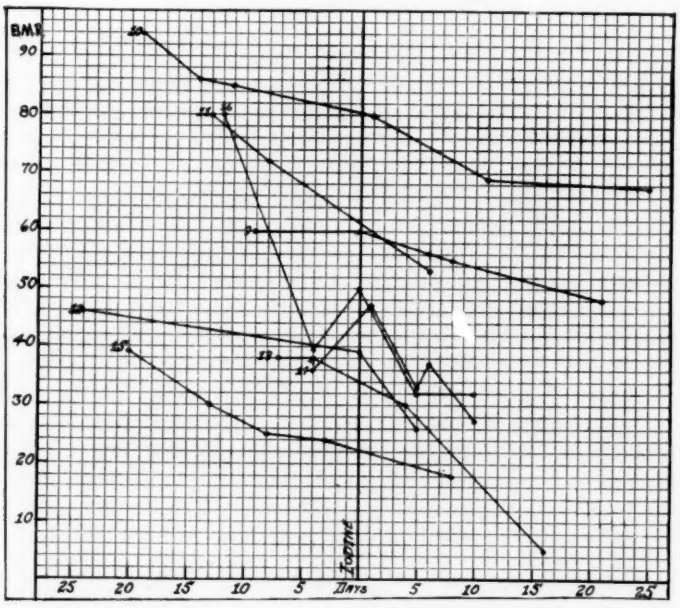

Chart 2.—Curves of basal metabolic rate in cases of toxic adenoma, 9 to 16 inclusive, in which the patients were treated with iodine.

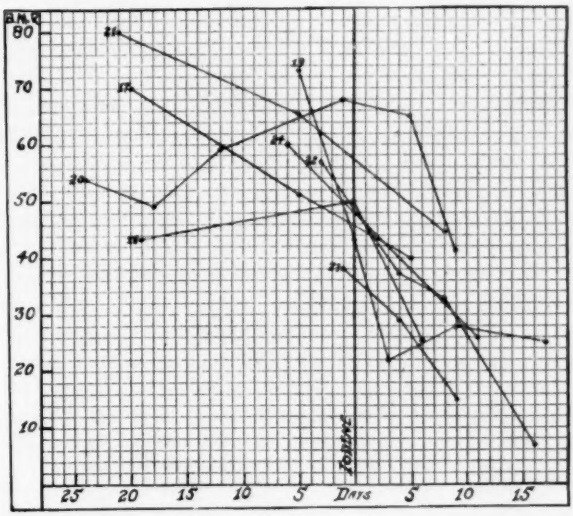

Chart 3.—Curves of basal metabolic rate of cases of toxic adenoma, 17 to 24 inclusive, in which the patients were treated with iodine.

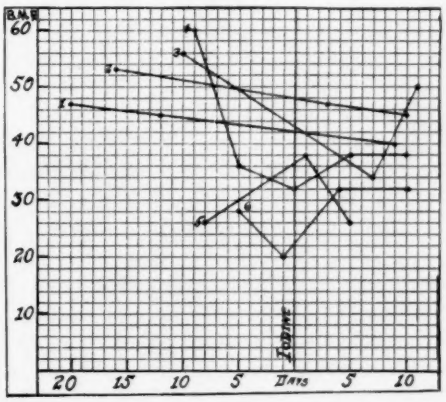

Chart 4.—Curves of basal metabolic rate in six cases of toxic adenoma in which the patients showed little or no response to iodine.

tion). It is seen that 6 of the 30 cases showed a reduction of less than 25 per cent; 9 showed a reduction of from 25 to 49 per cent; 8, a reduction of from 50 to 74 per cent, and 7, a reduction of from 75 to 100 per cent. Twenty-four showed a 25 per cent, or greater, reduction of the basal metabolic rate, and, with two exceptions, these cases have been included in the group showing a favorable response to iodine. The exceptions (cases 3 and 5, chart 4), although they showed a reduction in the basal metabolic rate of 50 and 42 per cent, respectively, have been included in the group showing no response to iodine, because clinical signs of improvement were absent. Conversely, two cases (cases 9 and 10, chart 2) that showed a reduction of the basal metabolic rate of less than 25 per cent have been included in the group showing a response to iodine, because there was marked remission of the clinical signs and symptoms of the disease. In this connection, it is important to

TABLE 2.—*Comparison of Percentage of Reduction of Basal Metabolism in Twenty-Four Cases Each of Toxic Adenoma and Exophthalmic Goiter Showing Favorable Response to Iodine*

Percentage of Reduction to Normal (+10)	Number of Cases	
	Toxic Adenoma	Exophthalmic Goiter
Less than 25	2	0
20 to 50	8	7
50 to 75	7	11
75 to 100	7	6

note that while the basal metabolism has been selected for the purposes of illustration as the best single evidence of the effect of iodine on these patients, it is not the only guide. In addition to the drop in basal metabolism, these patients exhibited a decreased pulse rate, gain in weight, lessened nervousness, amelioration of the cardiac symptoms and other clinical evidences of improvement.

In table 2 is shown a comparison of the degree of reduction of the basal metabolism in the twenty-four cases of toxic adenoma in which the patients showed the effect of iodine and in twenty-four unselected cases of exophthalmic goiter in which the patients showed the same favorable response to this drug. The average drop in the group of toxic adenoma was 22 points and in the exophthalmic group 30 points, while the average percentage of reduction of the basal metabolism was 58 and 64, respectively. Chart 5, in which are charted the last basal metabolic rates previous to the administration of iodine and the minimum rates after its administration, illustrates the similarity of response to iodine by patients with exophthalmic goiter and by those with toxic adenoma.

In four cases, there was a relapse or an escape from the effect of the iodine, and the previous or a worse clinical condition was noted. In two instances the relapse was associated with the discontinuance of

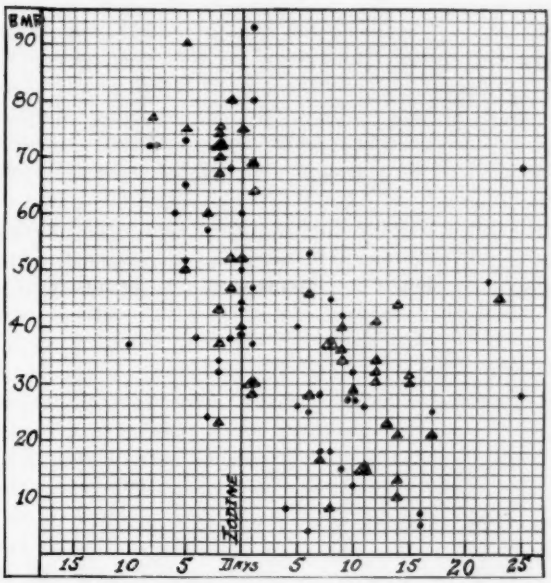

Chart 5.—Comparison of basal metabolic rates before and after administration of iodine in twenty-four cases of toxic adenoma and in twenty-four cases of exophthalmic goiter. The last basal metabolic rate before the administration of iodine and the minimum rate after this medication are charted. The dots indicate cases of toxic adenoma; the triangles, exophthalmic goiter.

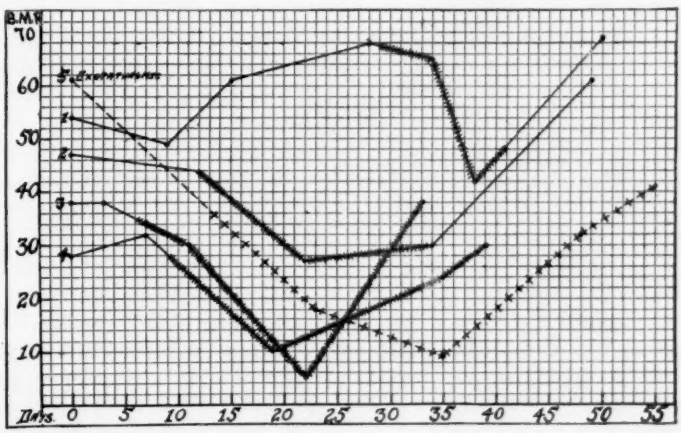

Chart 6.—Curves of basal metabolic rate in four cases of toxic adenoma showing relapse following discontinuance or prolonged use of iodine (cases 1 and 2 and cases 3 and 4 respectively). A similar curve in a case of exophthalmic goiter is shown for comparison (case 5). Cross hatching indicates the period of iodine administration.

iodine, and in two cases, with the long continued use of this drug. In all four cases the relapses followed initial remissions and were similar to those seen in cases of exophthalmic goiter under similar circumstances. Chart 6 shows the curves of the basal metabolic rates in these four cases, and for comparison a similar curve has been added in a case of exophthalmic goiter in which a relapse occurred following the prolonged use of iodine.

Patients with toxic adenoma not treated with iodine did not show the characteristic sudden drop in the metabolic rate and remission in clinical signs and symptoms seen in the patients treated with iodine.

COMMENT

The results presented in this paper indicate that patients with toxic adenoma, previously untreated with iodine, respond to its use in essentially the same way as patients with exophthalmic goiter. It is true that the basal metabolic rates do not show the same uniformity of drop following the administration of iodine or, on the average, as marked a drop as in selected cases of exophthalmic goiter. However, it should be borne in mind that the cases of toxic adenoma reported here are an unselected group, and that the results compare favorably with those obtained in a similarly unselected group of patients with exophthalmic goiter observed concurrently. It is also probable that had an opportunity been given for further determinations following the use of iodine, many of the patients would have exhibited a further drop in the basal metabolism. The fact that many had improved so remarkably that it seemed unwise to delay further the operative treatment indicates the degree of improvement. Further, the fact that similar clinical observations were made in forty-eight additional cases adds strong supplemental evidence of the favorable effect of the iodine in toxic adenoma. It is possible that larger doses of iodine might have caused a greater response in some of the more toxic cases, particularly in those in which the basal metabolism was high. As, however, a uniform dose of compound solution of iodine, 5 minims (0.3 cc.), three times a day, was employed to maintain standard conditions, this factor remains undetermined.

Not only was a similarity observed between toxic adenoma and exophthalmic goiter as far as the favorable response to iodine is concerned, but a similarity in the lack of response was likewise noted. A certain proportion of the patients with toxic adenoma failed to respond to iodine, as do a certain number of patients with exophthalmic goiter. Finally, the patients with toxic adenoma showed the same kind of relapse when iodine was discontinued and the same escape from its effect when the drug was long continued as was seen in the exophthalmic form of the disease. It would seem justifiable to conclude that whatever difference exists in the patient's response to treatment with iodine in toxic

adenoma and in exophthalmic goiter, it is merely a quantitative and not a qualitative one. Apparently, no essential difference in the pathogenesis of these two types of thyrotoxicosis can be assumed on the basis of the patient's response to treatment with iodine.

Occasional cases of toxic adenoma in which the patient responded favorably to iodine were reported in earlier articles on the action of iodine in exophthalmic goiter;[2] Boothby[3] has stated that certain patients with hyperfunctioning adenomatous goiter improve after the administration of this drug. The explanation of the effect in such cases has generally been considered unsettled. Since this work was begun, however, two reports[4] have appeared in which the observations are essentially in accord with ours, as are the conclusions of the authors. In fact, the average degree of drop in the basal metabolism in the cases reported by Starr in magnitude approaches even more closely that seen in exophthalmic goiter.

This response by patients with toxic adenoma to treatment with iodine, so essentially similar to that seen in exophthalmic goiter, cannot be explained on the basis of incorrect diagnosis, granting for the present that an acceptable differential diagnosis uniformly exists. All of our patients presented the clinical criteria said to be necessary for the diagnosis of toxic adenoma. They came from a region in which this condition is common, and were seen in a clinic in which the staff was familiar with this form of the disease. The pathologic observations were those commonly accepted as being characteristic of toxic adenoma, granting that such a pathologic differentiation exists. Finally, the independent report of essentially similar results from three widely separated clinics makes the likelihood of error based on mistaken diagnosis extremely improbable.

Of course, spontaneous improvement occurs in patients with toxic adenoma, but it also occurs in patients with exophthalmic goiter, and this fact may have some influence on the results obtained in both forms of the disease.

The reason for the quantitative difference in the response of patients with these two forms of the disease to treatment with iodine is undetermined. That it bears a relation to possible quantitative differences in the pathologic changes in the thyroid gland seems probable. The

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2. Mason, E. H.: Iodine Therapy in Toxic Goiter, Tr. A. Am. Phys. **39**:174, 1924.

3. Boothby, W. M.: The Use of Iodine in Exophthalmic Goiter, Endocrinology **8**:727 (Nov.) 1924.

4. Graham, A., and Cutler, E. C.: Exophthalmic Goiter and Toxic Adenoma. Similarity of Response to Iodine, Ann. Surg. **84**:497 (Oct.) 1926. Starr, Paul: The Course of Hyperthyroidism Under Iodine Medication, Arch. Int. Med. **39**:520 (April) 1927.

qualitative changes which undoubtedly occur may play no direct part in the response to treatment, except as they modify quantitatively the changes common to both forms of the disease. The reason for the lack of response to iodine in occasional cases of both forms of the disease is not clear, and this problem, which may have a bearing on pathogenesis, awaits solution.

That patients with toxic adenoma have a relapse associated with the discontinuance of iodine or its prolonged use, following initial improvement, is of great importance aside from the fact that in this way they behave like patients with exophthalmic goiter. It explains completely, it seems to us, the widespread misconception that iodine initiates toxicity in cases of adenomatous goiter that previously were not toxic. After initial and unrecognized improvement, patients in whom unrecognized and often mild thyrotoxicosis has existed prior to the administration of iodine develop an exacerbation of symptoms associated with the discontinuance or prolonged use of the iodine. The same phenomenon occurs in cases of exophthalmic goiter, and the emphasis which has been focused on its occurrence in adenomatous goiter, together with the mistaken interpretation that has been made, has served to increase generally the belief in a fundamental difference between these two types of the disease. In contrast with this mistaken interpretation of the action of iodine, Graham and Cutler [4] have recently reported that they failed to produce toxicity by giving iodine to patients with adenomatous, previously nontoxic, goiter. On the basis of our present knowledge, it seems improbable that iodine ever causes toxicity in a patient with a nontoxic adenomatous goiter, no matter in what doses the drug is used.

SUMMARY AND CONCLUSIONS

The response to treatment with iodine in thirty unselected patients with toxic adenoma who were previously untreated with iodine was essentially the same as that seen in unselected cases of exophthalmic goiter. Whatever differences exist are apparently quantitative, not qualitative. No essential difference in the pathogenesis of toxic adenoma and exophthalmic goiter can be assumed to exist on the basis of this response to treatment with iodine.

CHRONIC ULCERATIVE COLITIS WITH REFERENCE TO A BACTERIAL ETIOLOGY

EXPERIMENTAL STUDIES *

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Chronic ulcerative colitis is an involvement of the large intestine and is of unknown etiology. The disease usually begins in the rectum, sometimes at the mucocutaneous border of the anus; it may remain localized in the rectum or it may extend upward. Anatomically, the process is characterized by primarily involving the mucosa, the condition varying from edema and hyperemia with easy bleeding to miliary abscesses with subsequent discrete, petechial ulcers and "pocklike" scarring.[1] In some instances, there is an extension to the other layers of the intestine, resulting in the narrowing of the lumen of the affected part by extensive fibrosis. Myocardial changes and metastatic involvement of joints may occur.[2] Clinically, this disease is characterized by diarrhea—continuous or intermittent—with blood, pus, mucus, emaciation, debility, progressive anemia and at times pyrexia.

From time to time numerous investigators in different, and sometimes widely divergent, fields have made varied attempts to ascertain the etiologic factor, at least in part, of this condition. Impressions may have been gained, but definite conclusions have never prevailed in the light of subsequent experience and investigation.

The damage caused by this disease, the poor prognosis and the unsatisfactory management and treatment have led to another study with a view to determining, if possible, a bacterial etiology.

Specifically, the purpose of this study was to isolate bacteria, not including colon bacilli, from the bases of ulcers and from the mucosa when ulcers were not present in cases of acute exacerbations of chronic ulcerative colitis, with a view to establishing the consistent presence and preponderance of a definite bacterium; also to study the results in

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1. Buie, L. A.: Chronic Ulcerative Colitis, J. A. M. A. **87**:1271 (Oct. 16) 1926.

2. Brown, T. R.: Some Observations on Chronic Ulcerative Colitis, Ann. Clin. Med. **4**:425, 1925.

rabbits following the intravenous administration of organisms thus isolated and from other sources. Incidentally, a small comparative study was made of the flora of the human colon when normal and when the seat of ulcerative colitis.

Aerobic and anaerobic streptococci isolated from feces and from the mucosa of the sigmoid of apparently normal persons, anaerobic streptococci from cases of ulcerative colitis, as well as more organisms from sources other than the intestine, are being studied further and will be the subject of a subsequent report.

METHODS OF STUDY

Fourteen cases of acute exacerbations of chronic ulcerative colitis were studied. Each patient was given two enemas: one, during the early night preceding the day of examination, the other in the morning, one hour before the investigation. Immediately preceding the examination, the anus was cleansed with a preparation of green soap and water followed by a 1:1,000 solution of mercuric chloride. A sterile sigmoidoscope was then inserted. If any excreta—blood, mucus, pus, feces—were encountered in spite of these efforts, they were aspirated by means of a water suction pump, through a sterile aspirator inserted through the sigmoidoscope. Sterile swabs then cleansed that part of the involved intestine from which material was to be secured for bacteriologic study. Finally, specially prepared swabs[3] were introduced into the sigmoidoscope; with these the bases of ulcers were explored, and when ulcers were not present, the hyperemic, edematous, easily bleeding, friable mucous membrane was scraped.

Two, three and sometimes four swabs were employed during each examination. Each swab was introduced into a warmed tube of Rosenow's dextrose brain broth immediately after use. These tubes were incubated at 37 C. for from six to twenty-four hours; that is to say, at least one tube in each case was incubated for six hours; the others remained in the incubator for twenty-four hours.

From each tube smears were made and stained by Gram's method for the purpose of ascertaining, morphologically, the types of organisms present.

There was a deviation from this procedure in one instance. In this case, following the administration of enemas and an anal cleansing, a sterile rectal tube was inserted for a distance of 10 cm. A viscid, mucopurulent, sanguineous excretion was secured. A loopful of this mixed material was placed in each of several warmed tubes of dextrose brain broth, and incubated; subsequently, smears were made in the manner as already described.

The work of isolating the organisms was next performed. This was done by the blood agar plate method. The mediums employed and the procedure followed in this method were essentially the same as those described and used by Brown in his monograph on streptococci,[4] with the following addition: plates were made from six as well as from twenty-four hour cultures.

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3. A cotton swab is attached to a 13 inch iron wire applicator. This is enclosed within a glass tube 11 inches long; the purpose of the latter is to assist in preventing the swab from touching any other than the desired part.

4. Brown, J. Howard: The Use of Blood Agar for the Study of Streptococci, Monograph 9, Rockefeller Inst. M. Research, 1919, p. 6.

These plates were incubated over night. On the following morning, they were studied for colonies with beta and unquestioned alpha zones. The plates were then refrigerated for twenty-four hours, and at the end of that period studied again, especially for colonies with alpha and gamma zones, and the number of each variety was ascertained. The alpha, beta and gamma classification used was that described by Brown.[5] The isolated colony was inoculated into dextrose brain broth and after twenty-four hours into pancreatic digest bouillon. After twenty-four hours' incubation, cultures were made from the latter on blood agar slants for stock and to secure material for the ascertaining of encapsulation by the india ink method; sugar fermentation and bile solubility tests were then performed.

The bile solubility test was performed in the manner described in the "Medical War Manual no. 6, Laboratory Methods, U. S. Army." The india ink method of determining encapsulation was done by mixing a loopful of material from a heavy twenty-four hour blood agar slant growth with a loopful of india ink and covering the moist preparation with a coverslip. This was examined immediately thereafter for the presence of a light halo (capsule) about the organism.

The sugar fermentation tests were performed in the following manner: Pure cultures were inoculated into mediums for fermentation tests within ninety-six hours after isolation. The test mediums were inoculated from pure cultures in pancreatic digest broth, a sugar-free medium, in which the organism grew abundantly. Pancreatic digest broth was also used as the basic medium for the fermentation tests. The test substances were dextrose, maltose, lactose, saccharose, raffinose, inulin, mannite and salacin autoclaved in 10 per cent acqueous solution and then added aseptically to the broth so as to make about a 1 per cent solution of the test substance in the broth. Milk was also used as a test medium. Cultures in the test mediums were incubated five days and then tested for acid production by the addition of a couple of drops of brom cresol purple solution to each tube. In the tests in which the indicator showed a variation from the original purple to a definite yellow, the cultures were regarded as fermented.

Rabbits weighing about 1,600 Gm. were used in this study. Great care was taken in their selection; they came from good stock and had never been used in any other experimental study. During the period of observation prior to their use, which varied from four days to weeks, they never appeared ill, were free from diarrhea, and grew consistently on a ration consisting of hay, oats, lettuce, cabbage and sprouts.

Reference has been made already to the over night incubation of dextrose brain broth inoculated with the desired colonies secured from blood agar plates. Such cultures were intravenously injected into rabbits in varying dosages. In some instances, one dose was administered; in most cases, more than one dose was given. In second and subsequent injections, the cultures used on each occasion were twenty-four hour growths in dextrose brain broth of the desired organisms secured from blood agar slant stock cultures; the second and subsequent injections were administered in varying dosages at frequent but irregular intervals. A total amount of from 2 to 15 cc. was given. In two instances, mixed cultures were administered. These were originally fished from beta zoned colonies in blood agar plates and grown in dextrose brain broth for twenty-four hours. When subsequent doses were administered, the cultures were prepared from blood agar slant stock cultures as heretofore described. The organisms present in

5. Brown, J. Howard: The Use of Blood Agar for the Study of Streptococci, Monograph 9, Rockefeller Inst. M. Research, 1919, p. 8.

these mixed cultures were isolated and individually studied; they proved to be *Bacillus coli* and alpha zoned chain-forming streptococci. A total of from 1.5 to 6 cc. was administered.

B. coli was isolated from ulcers in a case of amebic dysentery as well as from a normal sigmoid. *B. dysenteriae* (Flexner and Shiga), a beta hemolytic streptococcus from the uterus of a human being suffering with puerperal sepsis and alpha hemolytic streptococcus secured from my throat, as well as a dead culture of a beta hemolytic streptococcus from a case of scarlatina, were injected into rabbits and studied in the manner already described. Dosages varying from 0.01 to 10 cc. were administered.

Autopsies were performed on all animals that died or were killed. All viscera were examined carefully, and cultures of heart blood were taken and studied. Lesions were sectioned and later examined microscopically.

OBSERVATIONS

The primary dextrose brain broth cultures, without exception, were mixed. Morphologically, whether it was a six or a twenty-four hour culture, there was nothing characteristic about it other than a lesser or greater growth. In each instance there was a preponderance of gram-positive organisms. Gram stained smears from primary dextrose brain broth showed diplococcal, short and sometimes somewhat long chained arrangements of what appeared to be, on the basis of morphology, streptococci, small clumps of cocci, and rods suggestive of *B. welchii*. Gram-negative bacilli were present in abundance.

It was soon learned that the morphologic picture of the original or primary dextrose brain broth was not helpful; on the contrary, it was misleading. An abundance of gram-positive bacteria were invariably in evidence in stained smears. Yet it was so difficult to isolate any bacilli other than gram-negative bacilli on blood agar plates that in each of six cases an additional sigmoidoscopic examination was required, and in three other cases two additional examinations were necessary for the securing of more material for further attempts at isolation.

Because of these difficulties in isolation, freshly prepared blood agar plates from three cases of ulcerative colitis were placed in anaerobe jars for forty-eight hours. Invariably, colonies with beta zones predominated; surface colonies and sometimes colonies with gamma zones were present. The beta zoned colonies showed diplococcal and chain formation arrangements of streptococci; the surface colonies showed gram-positive bacilli (*B. welchii*), and the gamma zones evidenced gram-negative bacilli which fermented lactose and produced gas (*B. coli* group). These were contrasted with plates grown aerobically. These aerobic plates, in most instances, were dominated by gram-negative bacilli.

A similar interesting situation arose when material was secured from the mucosa of the sigmoids of three persons who had always been free, as far as could be ascertained, from diarrhea and organic disease of the

gastro-intestinal tract. These persons were prepared for examination, and the material was secured from them in exactly the same manner as in cases of ulcerative colitis. In these apparently normal persons, streptococci were not demonstrable on aerobic blood agar plates, although stained smears from dextrose brain broth showed many gram-positive diplococci and chains of streptococci not unlike those seen in cases of

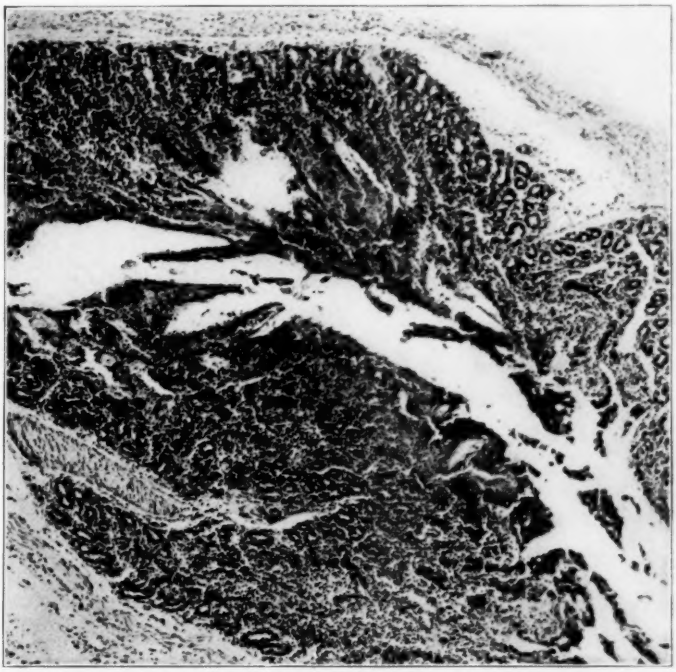

Fig. 1.—Colon of rabbit intravenously injected with a culture of streptococci from an alpha zoned colony. The organism did not ferment saccharose, raffinose and inulin. There is some infiltration and, in part, necrosis of mucosa with submucous inflammatory involvement. The lens used in the illustrations was: Zeiss, apochromate no. 10.

ulcerative colitis. Here, too, aerobically, surface, gamma and sometimes beta zoned deep colonies prevailed which proved to be gram-negative bacilli. Yet, when plates were placed in anaerobe jars for forty-eight hours, colonies similar to those noted on the plates grown anaerobically from cases of ulcerative colitis were present, except that in the latter group of cases, possibly more surface colonies of gram-positive bacilli (*B. welchii*) were found.

No alpha zoned colonies were noted on the plates incubated anaerobically with material either from apparently normal persons or from persons with ulcerative colitis. Brown, however, points out that "under anaerobic conditions alpha type streptococci and pneumococci produce beta zones." [6]

In other words, other than an apparent increase in *B. welchii* on anaerobic plates and the presence of streptococci in aerobic plates in cases

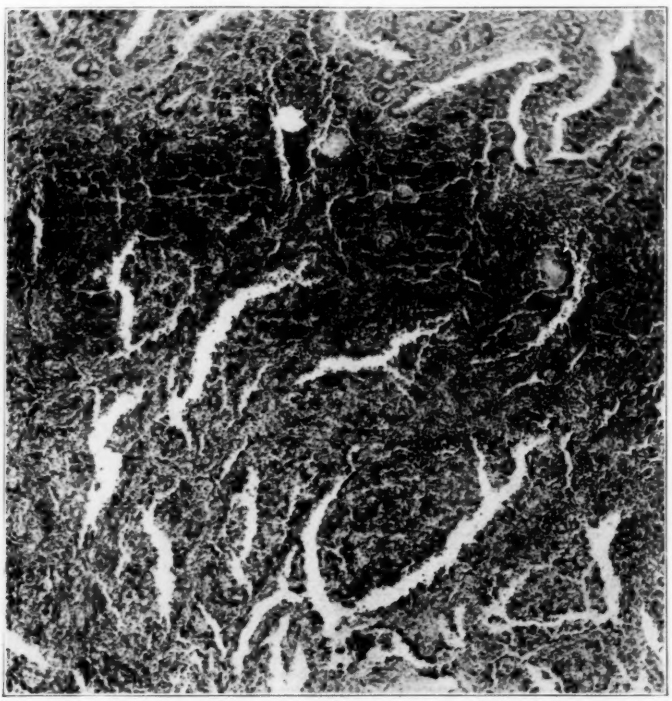

Fig. 2.—Rectum of rabbit intravenously injected with an alpha zoned streptococcus, diplococcal in morphology, and not fermenting inulin and mannite (Bargen's criteria). There is marked infiltration of submucosa.

of ulcerative colitis, as contrasted with no demonstrable streptococci on aerobic plates from swabs from the thoroughly cleaned rectums and sigmoids of persons who did not present diarrhea or organic gastrointestinal disease, definite differences were not noted in this small com-

6. Brown, J. Howard: The Use of Blood Agar for the Study of Streptococci, Monograph 9, Rockefeller Inst. M. Research, 1919, p. 95.

parative group. Stained smears of primary dextrose brain broth cultures in this same small comparative group did not show any distinctive morphologic differences.

Stained smears from fecal suspensions from pancreatic digest broth made from dejected excreta of three patients who had not had diarrhea or organic gastro-intestinal disease, but who had taken considerable milk in their diet, showed a morphologic picture not unlike that seen in primary dextrose brain broth cultures from material secured from the bases of ulcers in cases of acute exacerbations of chronic ulcerative colitis.

Ten types of streptococci were isolated from thirteen cases (table 1). In the fourteenth, forms other than colon bacilli could not be isolated from three swabs which had been taken from the bases of ulcers on two separate occasions and after the examination of eighteen plates. Eight types presented alpha zones; two, beta zoned colonies.

To explain further: In three cases, an alpha zoned colony predominated, but in only one of these three instances was the organism a diplococcus that did not ferment inulin and mannite (Bargen's criteria). Incidentally, in the other case in which the bacterium meeting Bargen's description was isolated, it did not appear in predominance. In one case a beta hemolytic, chain-forming streptococcus was present in marked preponderance; in still another case, alpha and beta zoned colonies of chain-forming streptococci were about equally numerous and together represented only half of the total number of colonies present. Two cases showed a preponderance of beta zoned colonies which proved to be mixed, i.e., gram-negative bacilli predominated over a chain-forming streptococcus. Subsequent isolation resulted in the streptococci appearing as alpha zoned colonies on blood agar plates. In the remaining seven cases, colon bacilli (gram-negative bacilli which fermented lactose and produced gas) dominated the scene, appearing in varied types of colony forms with few streptococci present.

All of the cocci were insoluble in bile and did not show capsule formation. No changes occurred in the retesting of the organisms by the fermentation test within from two to six months after the original isolation. Variations did not occur in the morphologic pictures in liquid mediums after a similar period of time.

The streptococci isolated from material secured from the bases of ulcers in cases of acute exacerbations of chronic ulcerative colitis, as in streptococci isolated from other sources and other conditions, do not have any characteristic morphology within themselves. It should be emphasized that the appearance of a lancet-shaped, gram-positive diplococcus with little if any tendency to chain formation is not characteristic of any one type of streptococcus. This appearance had been observed, not only in the group which had failed to ferment inulin and

TABLE 1.—*Results of Intravenous Injection of Rabbits with Streptococci from Cases of Ulcerative Colitis*

Organism	Type Colony	Did Not Ferment	Number of Rabbits Injected	Dosage	Locations and Descriptions of Lesions	Diarrhea			
						Clinically		Autopsy	
						Blood	No Blood	Blood	No Blood
Streptococci (very long chains)	Alpha	Salicin, raffinose, mannite, inulin	12	No. 330, 1 dose, 5 cc.	Colon: hemorrhagic area 3 cm. long; rectum: ulceration; anorectal junction hemorrhagic and edematous; sections confirm	+	0	0	+
				No. 312, 4 doses, 15 cc.	Peritoneum: serosanguineous fluid; colon, rectum and anus entirely involved, lesions vary from hemorrhages to ulcers; sections confirm	0	+	+	0
				No. 311, 4 doses, 15 cc.	Ileum: submucous hemorrhages and ulcerations; sections show acute ulcers	0	0	+	0
				No. 354, 3 doses, 9 cc.	Peritoneum: serosanguineous fluid; duodenum ileum, rectum: ulcerations; cecum: hemorrhagic area; sections confirm	0	+	0	+ (mucus)
			Plus B. coli	No. 340, 2 doses, 6 cc.	Colon and rectum: ulcerations and submucous hemorrhages; sections confirm	+	0	+	0
				No. 344, 1 dose, 3 cc.	Living	0	0	0	0
				No. 347, 5 doses, 15 cc.	Ileum and jejunum: mucous and submucous hemorrhages; ulcerations in small intestine; sections confirm	0	0	0	0
				No. 318, 1 dose, 2 cc.	No lesions; animals died of septicemia	0	0	0	0
				No. 320, 1 dose, 5 cc.		0	0	0	0
				No. 328, 5 doses, 15 cc.		0	0	0	0
				No. 356, 4 doses, 15 cc.		0	0	0	0
				No. 348, 3 doses, 6½ cc.	Living	0	0	0	0
Streptococci (diplococci in morphology)	Alpha	Inulin and mannite	6	No. 238, 3 doses, 14 cc.	Colon injected; rectum: ulcerated; sections show inflammation of mucosa in former; in latter submucosa involved	0	0	0	0
				No. 313, 4 doses, 15 cc.	No lesions	0	0	0	0
				No. 315, 4 doses, 12 cc.		0	0	0	0
				No. 325, 4 doses, 15 cc.		0	0	0	0
				No. 306, 4 doses, 15 cc.		0	0	0	0
				No. 247, 2 doses, 8 cc.		0	0	0	0

Streptococci (morphologically—diplococci and short chains, later longer chains)	Alpha	Saccharose, raffinose, inulin	4	No. 211, 3 doses, 12 cc.	Heart: pericarditis with effusion, myocardial abscess; ileum: submucous hemorrhage; colon and rectum: submucous hemorrhages and ulcerations; sections confirm	0	+	+	0
				No. 74, 1 dose, 5 cc.	Colon: submucous hemorrhages and ulcerations; sections confirm	+	0	+	0
				No. 324, 1 dose, 5 cc.	No lesions	+	0	+	0
				No. 229, 4 doses, 15 cc.	Living	0	0	0	0
Streptococci, (chain formation) plus B. coli	Alpha	Lactose, milk acidified, saccharose, raffinose, inulin	2	No. 345, 1 dose, 3 cc.	Gallbladder: enlarged; cecum: hemorrhagic area: rectum: ulceration; sections confirm	0	0	0	+
				No. 346, 1 dose, 3 cc.	Cecum: ulceration; colon and rectum: ulcerations; sections confirm	0	0	0	0
Streptococci (diplococci)	Alpha	Mannite	6	No. 361, 4 doses, 14 cc.	Bronchopneumonia; colon and rectum: submucous hemorrhage and ulcerations; sections confirm	+ (?)	0	0	+ (mucus)
				No. 240, 1 dose, 8 cc.	Ileum: hemorrhagic area; colon: ulceration; gallbladder: enlarged; sections show involvement in mucosa and submucosa	0	0	0	+
				No. 257, 1 dose, 5 cc.	Colon: hemorrhagic patch; sections show mucosal necrosis with inflammatory reaction in submucosa	0	0	0	0
				No. 359, 5 doses, 15 cc.	No lesions	0	+	0	0
				No. 357, 5 doses, 15 cc.		0	0	0	0
				No. 224, 2 doses, 12 cc.	Living	0	0	0	0
Streptococci (few diplococci, chiefly short but later longer chains)	Alpha	Inulin	2	No. 376, 6 doses, 30 cc.	No lesions	0	0	0	0
				No. 377, 6 doses, 30 cc.		0	0	0	0
Streptococci (chain forming)	Beta	Inulin, mannite, raffinose	2	No. 338, 4 doses, 14 cc.	No lesions	0	0	0	0
				No. 349, 2 doses, 4 cc.		0	0	0	0

mannite (the same group had fermented all other test substances mentioned under "Methods of Study"), but in strains which fermented all but mannite. This morphology was similarly observed in a strain not fermenting inulin, although it fermented mannite. In a six to twelve hour culture in liquid medium of a streptococcal strain not fermenting saccharose, raffinose and inulin, and in a similar culture of another strain not fermenting saccharose, raffinose, inulin and lactose but acidifying milk, diplococci with virtually no tendency to chain formation were in

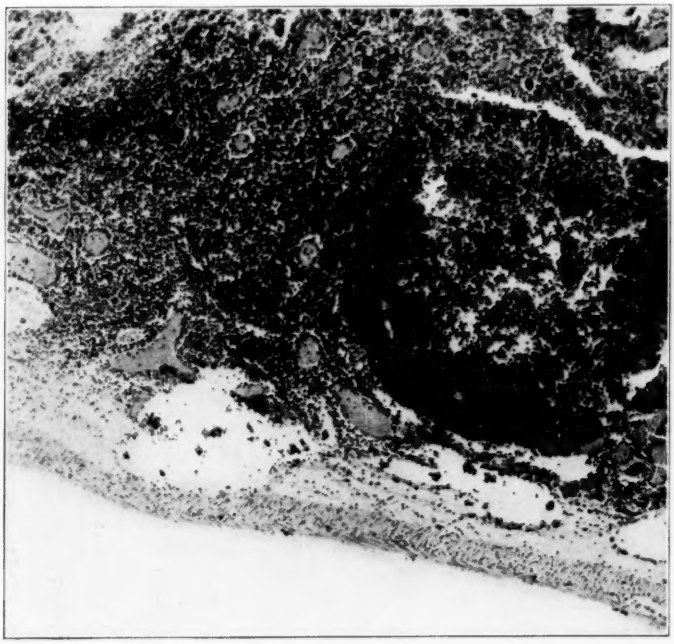

Fig. 3.—Rectum of rabbit injected intravenously with an alpha zoned, long chain forming streptococcus not fermenting salacin, raffinose, mannite and inulin. There is marked inflammatory reaction in the submucosa with lymphoid hyperplasia.

evidence in stained smears. Only after subcultivation in liquid mediums for twenty-four hours did the last two mentioned types show definite short chain formation.

Blood agar plates showing alpha colonies, after being refrigerated for about a month, in some instances evidenced *grossly* beta zoned colonies, but the microscopic examination revealed that the change was only apparent, for the blood corpuscles about the colonies were still

present. Frequently, gamma colonies on blood agar plates—plates kept at room temperature for about a week or more—showed some alteration in the appearance of the surrounding medium. Microscopically, however, it was evident that the colonies were neither alpha nor beta. In a few cases, stock cultures some months old were replated. No changes from the original were observed in the type of colony appearing then on the blood agar plates. It is submitted that the constancy of the

Fig. 4.—Rectum of rabbit injected intravenously with a culture from a beta zoned colony. The culture was mixed: colon bacilli and an alpha zoned chain forming streptococcus. The latter organism did not ferment lactose, saccharose, raffinose, inulin and acidified milk. There is mucosal necrosis, marked cellular infiltration in the submucosa and lymphoid hyperplasia.

colonies on blood agar plates as seen by *microscopic* examination, as well as the constancy of the morphology and of the fermentation tests, modestly confirms the work of Brown.[7]

7. Brown, J. Howard: The Use of Blood Agar for the Study of Streptococci, Monograph 9, Rockefeller Inst. M. Research, 1919, pp. 77-82.

Thirty-four rabbits were injected intravenously with seven types of organisms isolated from cases of ulcerative colitis after the manner already described in detail (table 1). Four rabbits are living; they did not show diarrhea or signs of illness at any time; thirty died or were killed and fourteen showed lesions, confirmed by section, varying from mucosal to mucous and submucous inflammatory involvements, with the muscularis sometimes invaded. The lesions ranged from hemorrhages and necroses to ulcerations. The locations of the lesions were as fol-

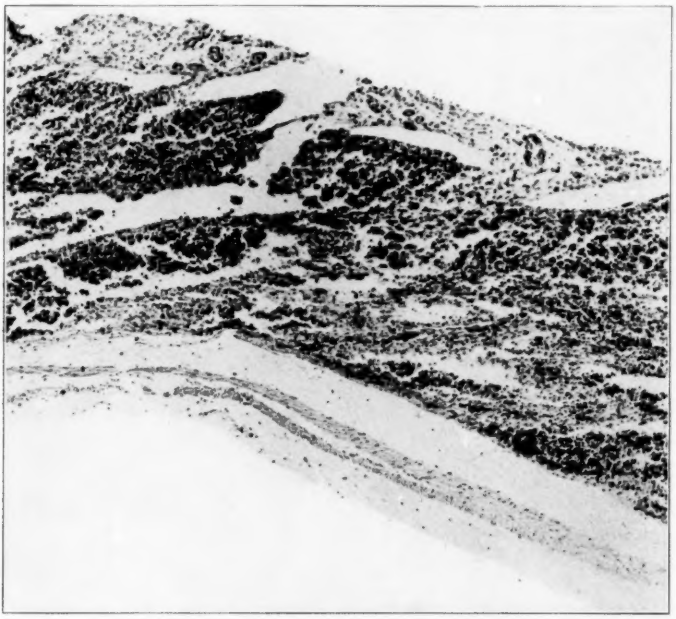

Fig. 5.—Colon of rabbit injected intravenously with an alpha zoned streptococcus, diploccal in morphology, which did not ferment mannite. The mucosa is destroyed. There is marked cellular infiltration in the submucosa.

lows: duodenum, 1; jejunum, 1; ileum, 5; appendix, 0; cecum, 3; colon, 10; rectum, 9; anus, 2.

Six of the thirty rabbits which came to autopsy were injected intravenously with a bacterium that met the following criteria: The organism presented itself on a blood agar plate as an alpha zoned colony; it appeared constantly as a diplococcus without tendency to chain formation; it did not ferment inulin and mannite, and, like all other organisms studied, it was insoluble in bile and did not present any capsules (Bargen's criteria). One rabbit of this group showed a lesion in the

colon and rectum, but did not give any evidence of diarrhea. The other five rabbits did not give any evidence of lesions or diarrhea. The remaining twenty-four rabbits were injected with other types of streptococci isolated from cases of ulcerative colitis. The lesions occurred exactly as already enumerated with reference to locations, with the exception of the one colon and one rectal lesion noted already. Eight of the twenty-four rabbits showed evidences of diarrhea about their bodies and cages; four showed blood and four did not. At autopsy, five rabbits showed loose, ill formed fecal material; in two of these the feces presented mucus, but blood was not seen in the feces of any of them; six rabbits showed evidences of diarrhea with blood. In all, twelve rabbits showed diarrhea in one way or another.

Twenty-two of the rabbits were injected intravenously with definite chain producing streptococci; ten showed lesions in the following locations: duodenum, 1; jejunum, 1; ileum, 4; appendix, 0; cecum, 3; colon, 6; rectum, 7; anus, 2.

In none of the thirty rabbits on which autopsy was performed were gross demonstrable lesions noted elsewhere than in the intestine, with the exception of pericarditis with effusion and a myocardial abscess in one, bronchopneumonia in another, and an enlarged gallbladder in each of two others. These five gross extra-enteric lesions occurred among the fourteen animals showing intestinal involvements.

Sixteen of the thirty rabbits intravenously injected with various forms of streptococci from cases of ulcerative colitis did not manifest any lesions at autopsy. They died from septicemia. The organisms injected were recovered from the heart blood.

Twenty additional rabbits were injected intravenously with seven types of bacteria from sources other than the bowel of patients with ulcerative colitis (table 2). Four rabbits are still living, and they did not show evidences of diarrhea or signs of illness at any time. Twelve of the sixteen rabbits that died or were killed showed lesions in the intestinal tract, confirmed by section. Grossly and microscopically, the lesions were not unlike those seen in rabbits injected with organisms from cases of ulcerative colitis; they varied from mucosal to mucous and submucous inflammatory involvements, with the muscularis sometimes invaded; the lesions ranged from hemorrhages to necroses or ulcerations. The locations of these involvements within the intestine, however, were different: duodenum, 0; jejunum, 1; ileum, 4; ileocecal valve, 1; appendix, 0; cecum, 6; colon, 4; rectum, 5; anus, 0. Two rabbits showed definite involvement of the gallbladder; one showed a definitely enlarged spleen and another, an hepatic abscess; otherwise no other viscera were grossly involved. In the few rabbits with extra-enteric lesions, the intestinal involvements were the more marked, pronounced or extensive, with the possible exception of the case of the hepatic abscess. Nine of the

TABLE 2.—*Results of the Intravenous Injections of Rabbits with Organisms from Other Sources*

Organism	Source	Number of Rabbits Injected	Dosage	Location and Description of Lesions	Diarrhea			
					Clinically		Autopsy	
					Blood	No Blood	Blood	No Blood
B. dysenteriae (Shiga)	Bacillary dysentery	3	A, 1 dose, 2 cc.	Colon: several hemorrhagic areas; section: involvement of mucosa	0	0	0	0
			No. 392, 6 doses, 2.3 cc.	Small intestine: hemorrhagic fluid; cecum: edematous; hepatic abscess	0	0	0	+
			No. 395, 5 doses, 1.1 cc.	Gallbladder: distended; cecum: ulcerations; sections: involvement of mucosa and submucosa in one, all layers in another	+	0	+	0
B. dysenteriae (Flexner)	Bacillary dysentery	4	No. 357, 1 dose, 2 cc.	Lesions in rectum? Not borne out by section	0	0	0	0
			No. 358, 1 dose, 3 cc.	Cecum: ulceration; confirmed by section	0	0	0	+
			No. 380, 1 dose, 2 cc.	Hemorrhagic fluid in small intestine	0	0	0	0
			No. 383, 6 doses, 3¼ cc.	Living				
B. coli	Amebic dysentery	2	No. 389, 1 dose, 3 cc.	Cecum: submucous hemorrhages and ulcers; sections confirm above	0	+	0	+
			No. 390, 1 dose, 5 cc.	Ileocecal valve: submucous hemorrhage; sections of both show involvement of mucosa and submucosa	0	0	0	0
B. coli	Normal sigmoid	2	No. B, 1 dose, 2 cc.	Terminal ileum: hemorrhage and pinhead ulcers; cecum: hemorrhagic area; sections confirm above	0	+	0	+
			No. C, 2 doses, 6 cc.	Ileum: hemorrhagic mucoid fluid; descending colon and rectum: submucous hemorrhages and ulcerations confirmed by sections	0	+	0	+
Streptococcus (alpha zoned colony)	Normal throat	2	No. E, 1 dose, 10 cc.	Rectal submucous hemorrhages; sections show mucosal necrosis	0	0	0	+
			No. D, 1 dose, 15 cc.	No lesions	0	0	0	0
Did not ferment salicin, raffinose, mannite, and inulin								
Streptococcus (beta zoned colony)	Human uterus: puerpal sepsis	4	No. 353, 1 dose, 2 cc.	Ileum: hemorrhagic patches; colon and rectum: several ulcers; confirmed by section	+	0	0	+
			No. 352, 3 doses, 8 cc.	Cecum: ulcerations; rectum: ulcerations	0	0	0	0
			No. 382, 7 doses, 3½ cc.	Jejunum and ileum: hemorrhages	0	0	0	0
			No. 379, 10 doses, 4 cc.	Living				
Streptococcus (beta zoned; dead culture; strain T.D.B.Y.)	Throat; scarlatina	3	No. 373, 3 doses, 8 cc.	Gallbladder: enlarged; ileum: ulcer; colon and rectum: ulcers; sections show mucosal necrosis with cellular infiltration in submucosa and muscularis	0	+	+	0
			No. 397, 4 doses, 4 cc.	Living				
			No. 400, 3 doses, 10 cc.	Living				

sixteen rabbits evidenced diarrhea with or without blood either clinically or at autopsy. Clinically, four animals showed diarrhea without blood; two, with blood. At autopsy, seven showed liquid feces in the colon without blood; two, with blood. Four rabbits did not show lesions, but died as a result of septicemia.

* * *

Bargen of the Mayo Clinic, working in Rosenow's laboratory, claims to have isolated a gram-positive diplococcus which he regards as the etiologic factor in idiopathic ulcerative colitis. He ascribes definite cultural characteristics to this organism which he is able to isolate, and which appears in preponderance in 80 per cent of his cases; it appears on a blood agar plate as an alpha zoned colony, forms groups of twos and fours, sometimes has a capsule, is bile-insoluble and does not ferment inulin and mannite but always ferments dextrose, maltose, lactose, saccharose, raffinose and salacin and acidifies milk. He adds, however,

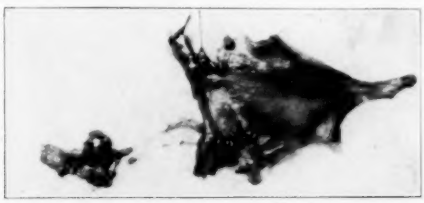

Fig. 6.—Rectum of rabbit injected intravenously with an alpha zoned streptococcus, chain forming, isolated from the author's throat. This organism did not ferment salacin, raffinose, mannite and inulin. The dark areas indicate submucous hemorrhages.

that after weeks or months, the reactions of the last six sugars may vary;[8] in other words, the nonfermentation of inulin and mannite by this organism is a constant character. The intravenous injection of rabbits and some dogs with dextrose brain broth cultures produced lesions varying from hemorrhages to ulcerations, primarily in the colon, in somewhat more than 30 per cent of the rabbits so treated.[8] No gross demonstrable lesions are reported elsewhere.

Diplococcus is merely a descriptive morphologic term. Many strains of streptococci under certain conditions grow as diplococci indistinguishable from that described by Bargen. As noted under "Observations" in this paper, several other varieties of streptococci from cases of ulcerative colitis gave similar appearances, especially in early cultures. In agree-

8. Bargen, J. A., and Logan, A. H.: Experimental Studies on the Etiology of Chronic Ulcerative Colitis: Suggestions for a More Rational Form of Treatment, Collected Papers of Mayo Clinic, 1925, no. 17, pp. 266-267.

ment with this opinion, Torrey stated that "Bargen sent me two of his strains (BB and HS), and in my opinion there is nothing in their morphology which is distinctive. The same morphological type is common in the human intestine in the feces of bottle-fed infants and in such material from adults taking considerable milk in their diet. The enterococcus may average somewhat larger, but there are no real distinctive morphological differences." [9]

Although Bargen reported his ability to isolate the diplococcus in 80 per cent of sixty-eight cases investigated, he mentioned having studied only twenty strains.[8] Presumably, the other strains were diagnosed on the basis of morphology only.

Diplococci morphologically and culturally similar to those described by Bargen are found not only in cases of ulcerative colitis, but in other

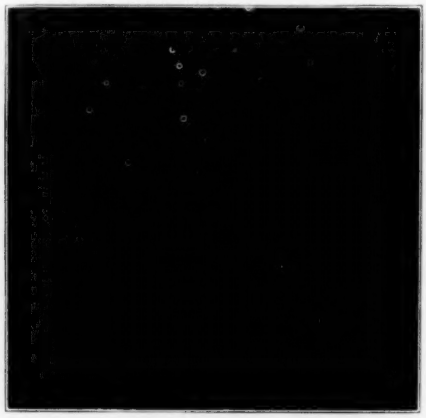

Fig. 7.—Blood agar plate showing pure culture of alpha zoned colonies. Viewed through a lens, the red blood cells contiguous to the colonies could be noted (Brown).

cases. Torrey reported that he had isolated this organism from the feces of a patient with mild cecitis.[9] Bargen stated that this organism cannot be isolated from feces. Denny and Frobisher,[10] working in this laboratory, have isolated similar cocci from the throats of four nephritic patients. These patients did not have diarrhea, and never suffered with organic disease of the digestive tract as far as could be ascertained.

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9. Torrey, J. C.: Bacteriology of the Human Colon with Particular Reference to Nonspecific Ulcerative Colitis, Tr. Am. Gastro-Enterol. A., 1927, in press; personal communication to the author.

10. Denny, E. R., and Frobisher, Martin, Jr.: Personal communication to the author.

It will be conceded that the diplococcus described by Bargen, when intravenously injected into rabbits and dogs, will produce lesions and diarrhea such as he has described. In reading Bargen's articles, however, it is not always clear whether he has injected mixed or pure

TABLE 3.—*Streptococci Isolated from Two Cases of Ulcerative Colitis not Intravenously Injected Into Rabbits*

Colony	Comment
Alpha zoned on blood agar plates	The organism did not ferment mannite, inulin, raffinose and lactose and acidified milk
Alpha zoned on blood agar plates	The organism did not ferment lactose, saccharose, raffinose and inulin and acidified milk
Beta zoned on blood agar plates	The organism did not ferment mannite, inulin, raffinose and lactose and acidified milk

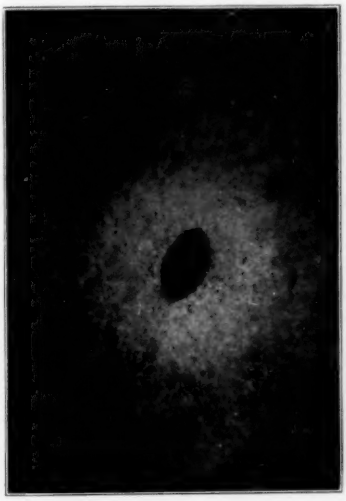

Fig. 8.—An alpha zoned colony from plate shown in figure 7, under low power. An area of hemolysis about colony is present, but closely adjoining the latter are red blood cells (Brown).

cultures. Since similar lesions can be produced with a number of different organisms, it can hardly be conceded that lesions produced by the injection of mixed cultures have a specific etiology. Furthermore, it does not appear in Bargen's communications that he performed any control experiments. He offers as controls the work of Rosenow and others, who working independently of Bargen on problems other than ulcerative colitis, have injected streptococci from other sources into lower animals. Apparently Bargen has not injected intravenously into lower animals, other forms or types of streptococci, in pure culture, isolated from the bowel of patients with ulcerative colitis in order to make a comparative study.

Isolation in pure culture of the diplococcus described by Bargen from an abscess in a protruding bowel of a patient with ulcerative colitis on whom an ileostomy had been performed does not necessarily mean that the organism isolated is the etiologic factor in this disease, since it may have been secondary.

N. W. Jones, of Portland, Ore., reported before the American Gastro-Enterological Association, on May ', 1927, that in a small study in collaboration with Benson and Menne, he was able to confirm Bargen's work. He permitted the author to copy the technic employed and to quote him. These investigators employed Rosenow's technic; they injected primary dextrose brain broth cultures intravenously into rabbits. These cultures contained the mixed intestinal flora from cases of ulcerative colitis. These results are subject to the criticism offered with reference to the injection of mixed cultures.

The vaccine filtrates used by Bargen in the treatment in these cases were made from the original [11] or primary dextrose brain broth cultures; hence, patients were receiving mixed autogenous vaccine filtrates. If it is assumed that Bargen's diplococcus in pure culture might be used in the making of filtrates or vaccines proper, the lack of abruptness in the cessation of symptoms and signs when they are used, their employment over a variable but fairly long period of time, the supplementing of vaccine therapy with many other usual forms of treatment, suggest that the favorable response to treatment reported by Bargen is a nonspecific, foreign protein reaction in a disease which presents a variable course and the acute exacerbations of which appear to be self-limited.

COMMENT AND SUMMARY

Fourteen cases of acute exacerbations of chronic ulcerative colitis have been studied with reference to a bacterial etiology.

Ten distinct types of streptococci were isolated in these cases. No one type was present in more than three cases. Eight varieties appeared as alpha zoned colonies on blood agar plates; two, as beta.

Seven types of these streptococci were intravenously injected into thirty-four rabbits, five of which produced lesions in these animals. Of thirty that came to autopsy, fourteen showed lesions, confirmed by section; these were primarily in the colon and rectum. Twelve rabbits manifested definite diarrhea with or without blood or mucus, clinically or at autopsy. Extra-enteric lesions were grossly demonstrable in each of four rabbits presenting intestinal involvements; in two, however, the major lesions were intestinal.

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11. Bargen, J. A., and Logan, A. H.: Experimental Studies on the Etiology of Chronic Ulcerative Colitis: Suggestions for a More Rational Form of Treatment, Collected Papers of Mayo Clinic, 1925, no. 17, p. 273.

Twenty other rabbits were injected intravenously with seven types of bacteria from sources other than the bowel in cases of ulcerative colitis. Of sixteen rabbits on which autopsy was performed, twelve showed lesions which grossly and microscopically were not unlike those seen in rabbits injected with organisms from cases of ulcerative colitis. However, the location of the lesions was different, a lesser number occurring in the rectum and colon and a greater number elsewhere in the intestinal tract. There was one extra-enteric lesion in each of four rabbits; in three rabbits the major lesions were intestinal. Nine rabbits manifested diarrhea with or without blood or mucus, clinically or at autopsy.

The author believes that there was no difference between lesions produced in the intestines of rabbits by the intravenous injection of organisms isolated from cases of ulcerative colitis or from other sources. Grossly and microscopically, all lesions were similar, differing only as to their location within the intestinal tract.

It was interesting to note that in sections of lesions stained for bacteria, a variety of types of organisms were found which, morphologically, were analogous to the mixed intestinal flora of the rabbit, regardless of the type of organism intravenously injected into the animal.

There are no distinctive differences, morphologically, between primary dextrose brain broth cultures from material secured from the bases of cases of ulcerative colitis and those from swabs from cleansed normal sigmoids. Only in some instances did there seem to be an increase in gram-positive organisms in the former, but such a picture was not characteristic; stained smears of broth suspensions of dejected excreta from apparently normal persons taking considerable milk in their diet also presented a preponderance of gram-positive bacteria and appeared to be identical, in morphology, to stained smears from the primary cultures of cases of ulcerative colitis.

In a comparative study of the bacterial flora of a small group of normal persons and of cases with ulcerative colitis, *B. coli, B. welchii* and streptococci preponderated in the latter type of cases. One cannot say, as a result of this study, what definite rôle the two former organisms play in the causation of this disease. The appearance of streptococci in predominance may mean one of two things: either they were able to escape the cleansing enemas and swabbing by hiding in the ulcers where they multiplied because of an environment favorable to their growth, or their increased presence may indicate that they may be in some measure etiologically responsible for this condition.

In view of the author's study, it is felt that Bargen has established that the streptococcus or diplococcus described by him, an organism

that morphologically is not characteristic of any one type of gram-positive coccus inhabiting the normal or diseased human intestine, can be isolated with some degree of frequency in cases of ulcerative colitis; and that when this diplococcus is injected into animals, lesions in the colon and rectum are produced. Bargen has not performed control experiments to establish specificity. His vaccine therapy appears to be non-specific.

Finally, in view of the fact that ten varieties of streptococci were found in fourteen cases of ulcerative colitis, that similar lesions were produced and chiefly produced in the colon and rectum of rabbits intravenously injected with any one of five types, and that in other rabbits intravenously injected with other organisms from other sources similar lesions were produced in the colon and rectum, I submit the statement that the bacterial etiology of ulcerative colitis is still undetermined.

The Johns Hopkins Hospital.

ABSTRACT OF DISCUSSION

Dr. J. Howard Brown, Baltimore: It deserves to be emphasized that Dr. Paulson's work is valuable because positive lesions were secured in animals. If a lesion had not been secured, it might well be said that failure to follow the technic which has been described by Dr. Bargen, who in turn followed Dr. Rosenow, might be the cause of the failure to duplicate the results. At the beginning of this work, Dr. Paulson was rather enthusiastic over the work which Dr. Bargen had done, and it was not with a view to discrediting that work that he undertook his experiments. At times while he was producing lesions he was inclined to believe that he was getting complete confirmation of Dr. Bargen's results, and it was only after he was urged to try other streptococci and to study their characteristics rather minutely that he took the attitude which he now has in regard to it.

In Dr. Bargen's work, there is, it seems, not a sufficient number of controls; that is, he points to the fact that in numerous rabbits injected with streptococci by other persons these lesions have not been described. However, it must be remembered that the mere statement that lesions were found in the appendix, in the heart or elsewhere, and that lesions were not found in other parts of the body cannot be taken as a control for work in which this particular lesion is being sought. I think Dr. Bargen's work suffers for lack of controls inoculated by himself with streptococci of other characteristics than that which he describes.

Dr. Paulson emphasizes the fact that the streptococci found in these ulcers do not have a characteristic morphology; that is to say, the streptococci are very much like pneumococci in appearance; they are diplococci. Most streptococci grow as diplococci on the mucosa or on solid mediums and some of them in fluid mediums, so there is nothing particularly characteristic about that form. It is only after careful study of these streptococci in the blood agar plates and their fermentation reactions that they can be identified or differentiated one from another. There has been no appreciable variation in the cultural characters of these organisms since the time of their isolation. The fact that definite lesions were secured

indicates that more than one variety of streptococcus and possibly more than one other kind of organism can produce such lesions, so that ulcerative colitis can hardly be regarded as specific in the sense that it is produced by a single kind of streptococcus.

DR. FRANK SMITHIES, Chicago: Were any nonbacterial proteins used intravenously, such as egg-white, peptone solutions and the like? Years ago, Vaughan and others showed the frequency with which such materials injected into the blood stream would produce lesions in the alimentary tract.

DR. A. F. R. ANDRESEN, Brooklyn: What Dr. Smithies says suggests to me three cases which I have seen in the last six months that presented the characteristics of an ulcerative colitis, and which were apparently due to food allergy; in these cases, the condition cleared up promptly when the offending food proteins were eliminated from the diet. Their cultural characteristics varied in each case, and I think that in the study of chronic ulcerative colitis one has to be on the lookout constantly for that type of case.

DR. WALTER C. ALVAREZ, Rochester, Minn.: The work of Dr. Paulson shows the need for further study before it can be determined just what relation Bargen's organism has to colitis. The problem is complicated by the fact that secondary invaders are commonly present in the lesions; in fact, Dr. Buie, the proctologist at the Mayo Clinic, differentiates clearly between certain ulcers produced by the diplococcus and others nearby produced by or contaminated by secondary invaders. A point that has impressed me is that the diplococcus has been isolated in pure culture from pinpoint ulcerations found on the mucous membrane of the ileum, as it prolapsed through an ileostomy wound. I feel that doubts expressed about the specificity of this organism should not make one lose sight of the fact that Dr. Logan, who for years made a particular study of this type of colitis and felt almost hopeless about curing it, now believes with Dr. Bargen that with the help of the vaccine filtrate it can frequently be either cured or certainly well arrested. I have seen some of the patients return after a year, fat and healthy, without ulcers and with haustra returning, and I think much has been achieved.

DR. MOSES PAULSON: In answer to Dr. Smithies' question, I can say that the injection of foreign proteins was suggested by Dr. J. Howard Brown on several occasions, but I never reached that point in this research for there was always so much to do. I am continuing with the problem, and I plan to inject into rabbits foreign proteins to see what lesions will occur in these animals, by way of comparison. However, I virtually did this when a dead culture of streptococci isolated from a case of scarlatina was injected into a rabbit, and lesions were secured, as detailed in the paper. With reference to Dr. Alvarez's point that Dr. Bargen was able to demonstrate in the original or primary culture a pure culture of the diplococcus or streptococcus described by him (Bargen) from an abscess in a protruding intestinal loop resulting from an ileostomy, this does not prove anything, for, as I have already mentioned in my paper, this organism may be purely secondary. It reminds me of the recent experience of Dr. Small of the Philadelphia General Hospital. He isolated from the blood stream in patients with rheumatic fever a type of streptococcus that he felt was the causative factor, because when he injected the organism intravenously into rabbits, he obtained characteristic pathologic processes of the joints and heart only to be told in a "Current Comment" of *The Journal of the American Medical Association* that similar lesions have been obtained in lower animals by the injection of other forms of streptococci isolated from patients with rheumatic fever.

Bargen deserves much credit for stimulating interest in this work. His experience with his vaccine in 385 cases reported at the last meeting (May 3, 1927) of the American Gastro-Enterological Association is interesting, but the good results he reports cannot be accepted as specific. My reasons, briefly, are first, as proved in this research, the specific organism of ulcerative colitis is yet to be discovered; second, Bargen made his vaccine filtrate from original or primary cultures, and therefore he was using a mixed vaccine or vaccine filtrate; third, his good results were obtained after varying but long periods in a disease which has natural remissions; and fourth, his patients received treatment in addition to the use of his vaccine therapy.

LOGARITHMIC TABLES FOR COMPUTING THE SURFACE AREA OF THE BODY ACCORDING TO DUBOIS' FORMULA *

C. H. McCLOY
NEW YORK

In 1916, Dubois and Dubois [1] published a formula for the computation of the surface area of the body and presented a chart from which one could read the approximate surface area from the coordinates of height and weight if given in metric units. This chart permitted one to read the surface area to within approximately 150 square centimeters.

Boothby and Sandiford [2] and Feldman and Umanski [3] publish nomograms for computing the surface area. In my experience, these have given large errors for the larger surface areas. These errors would be of small significance in ordinary clinical work, but they introduce an element of uncertainty in research work of any degree of refinement.

Owing to the use of surface area in the computation of normal vital capacity and in research in the field of basal metabolism, a means of ascertaining surface area quickly and accurately from either English or metric units of measurement is desirable. For those working extensively in this field, it would probably be an economy of time to prepare large charts on fine coordinate paper, like the smaller chart of Dubois and Dubois.[1] For physicians and health workers who may desire from time to time to compute the surface area accurately and rapidly, I have prepared the following tables of logarithms. These will give the surface area to within 10 square centimeters, and, when one is acquainted with their use, they may be used rapidly.

The formula of Dubois and Dubois for the computation of the surface area is as follows:

$H^{.725} \times W^{.425} \times 71.84 =$ surface area in square centimeters, in which H is height in centimeters, and W is weight in kilograms. It is obvious that the logarithm of the surface area (S.A.) computed from metric measurements may be found from the following:

Log. S. A. = 0.725 (Log. Height) + 0.425 (Log. Weight) + Log. 71.84.

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* From the Department of Physical Education, National Council, Y. M. C. A.

1. Dubois and Dubois: Clinical calorimetry, Arch. Int. Med. **17**:863 (June) 1916.

2. Boothby and Sandiford: Boston Medical and Surgical Journal **185**:337, 1921.

3. Feldman and Umanski: Lancet **1**:273, 1922.

For English units of measurement, the logarithm of surface area (surface area being in square centimeters, but height and weight being in inches and pounds) would be as follows:

$$0.725\ (\text{Log.}\frac{\text{Height in inches}}{0.3937}) + 0.425\ (\text{Log.}\frac{\text{Weight in pounds}}{2.20462}) + \log.\ 71.84$$

Either of these processes is too involved for convenience. In the tables given below, this work has been condensed.

Table 1 gives the logarithm of (height in centimeters)$^{.725}$; table 2 gives the logarithm of ([weight in kilograms]$^{.425} \times 71.84$); table 3 gives the logarithm of $(\frac{\text{height in inches}}{.3937})^{.725}$; table 4 gives the logarithm of $[(\frac{\text{weight in pounds}}{2.20462})^{.425} \times 71.84]$; table 5 gives the antilogarithms for all resultant logarithms needed for the computation of surface area. To use these tables, the logarithm corresponding to the height of the individual should be added to the logarithm corresponding to his weight. In table 5 will be found the surface area.

EXAMPLES

Metric Units.—If height is 168 cm. and weight is 61 Kg., tables 1 and 2 are used.

168 cm.	= Log.	1.613
61 Kg.	= Log.	2.615
Sum =		4.228

In table 5, the antilogarithm of the logarithm 4.228 is 16,900, which is the surface area in square centimeters.

English Units.—If the height is 64 inches and the weight 104 lb., tables 3 and 4 are used.

64 inches	= Log.	1.603
104 pounds	= Log.	2.568
Sum	=	4.171

In table 5, the antilogarithm of the logarithm 4.171 is 14,830, which is the surface area in square centimeters.

TABLE 1.—*Logarithms of Height in Centimeters*

Log. (Height)$^{0.725}$ (Metric)											
Cm.	Log.	Cm.	Log.	Cm.	Log.	Cm.	Log.	Cm.	Log.	Cm.	Log.
100	1.450	120	1.507	140	1.556	160	1.598	180	1.635	200	1.638
102	1.456	122	1.512	142	1.560	162	1.602	182	1.639	...	.....
104	1.462	124	1.518	144	1.565	164	1.606	184	1.642	...	.....
106	1.468	126	1.523	146	1.569	166	1.610	186	1.645	...	.....
108	1.474	128	1.528	148	1.573	168	1.613	188	1.649	...	.....
110	1.480	130	1.533	150	1.577	170	1.617	190	1.652	...	.....
112	1.486	132	1.537	152	1.582	172	1.612	192	1.655	...	.....
114	1.491	134	1.542	154	1.586	174	1.624	194	1.659	...	.....
116	1.497	136	1.547	156	1.590	176	1.628	196	1.662	...	.....
118	1.502	138	1.551	158	1.594	178	1.632	198	1.665	...	.....

TABLE 2.—*Logarithms of Weight in Kilograms*

Log. [(Weight) $^{0.425}$ × 71.84]

Kg.	Log.	Kg.	Log.	Kg.	Log.	Kg.	Log.	Kg.	Log.
18.0	2.390	35.0	2.513	50.0	2.578	65.0	2.627	80.0	2.665
18.5	2.395	35.5	2.515	50.5	2.580	65.5	2.628	80.5	2.666
19.0	2.400	36.0	2.518	51.0	2.582	66.0	2.630	81.0	2.667
19.5	2.405	36.5	2.520	51.5	2.584	66.5	2.631	81.5	2.669
20.0	2.409	37.0	2.523	52.0	2.586	67.0	2.632	82.0	2.670
20.5	2.414	37.5	2.525	52.5	2.587	67.5	2.633	82.5	2.671
21.0	2.418	38.0	2.528	53.0	2.589	68.0	2.635	83.0	2.672
21.5	2.423	38.5	2.530	53.5	2.591	68.5	2.637	83.5	2.673
22.0	2.427	39.0	2.533	54.0	2.593	69.0	2.638	84.0	2.674
22.5	2.431	39.5	2.535	54.5	2.594	69.5	2.639	84.5	2.675
23.0	2.435	40.0	2.537	55.0	2.596	70.0	2.641	85.0	2.676
23.5	2.439	40.5	2.540	55.5	2.598	70.5	2.642	85.5	2.677
24.0	2.443	41.0	2.542	56.0	2.599	71.0	2.643	86.0	2.679
24.5	2.447	41.5	2.544	56.5	2.601	71.5	2.644	86.5	2.680
25.0	2.450	42.0	2.546	57.0	2.603	72.0	2.646	87.0	2.681
25.5	2.454	42.5	2.548	57.5	2.604	72.5	2.647	87.5	2.682
26.0	2.458	43.0	2.551	58.0	2.606	73.0	2.648	88.0	2.683
26.5	2.461	43.5	2.553	58.5	2.607	73.5	2.650	88.5	2.684
27.0	2.465	44.0	2.555	59.0	2.609	74.0	2.651	89.0	2.685
27.5	2.468	44.5	2.557	59.5	2.611	74.5	2.652	89.5	2.686
28.0	2.471	45.0	2.559	60.0	2.612	75.0	2.653	90.0	2.687
28.5	2.475	45.5	2.561	60.5	2.614	75.5	2.654	90.5	2.688
29.0	2.478	46.0	2.563	61.0	2.615	76.0	2.656	91.0	2.689
29.5	2.481	46.5	2.565	61.5	2.617	76.5	2.657	91.5	2.690
30.0	2.484	47.0	2.567	62.0	2.618	77.0	2.658	92.0	2.691
30.5	2.487	47.5	2.569	62.5	2.620	77.5	2.659	92.5	2.692
31.0	2.490	48.0	2.571	63.0	2.621	78.0	2.661	....	.....
31.5	2.493	48.5	2.573	63.5	2.623	78.5	2.662	....	.....
32.0	2.496	49.0	2.575	64.0	2.624	79.0	2.663	....	.....
32.5	2.499	49.5	2.577	64.5	2.625	79.5	2.664	....	.....
33.0	2.502	....	.....	....	.....	....	.....	....	.....
33.5	2.504	....	.....	....	.....	....	.....	....	.....
34.0	2.507	....	.....	....	.....	....	.....	....	.....
34.5	2.510	....	.....	....	.....	....	.....	....	.....

TABLE 3.—*Logarithms of Height in Inches*

Log. $\left(\frac{\text{Height}}{0.3937}\right)^{0.725}$

Height Inches	Log.	Inches	Log.	Inches	Log.	Inches	Log.
40	1.455	50	1.525	60	1.583	70	1.631
41	1.462	51	1.531	61	1.588	71	1.636
42	1.470	52	1.537	62	1.593	72	1.640
43	1.478	53	1.544	63	1.598	73	1.645
44	1.485	54	1.549	64	1.603	74	1.649
45	1.492	55	1.555	65	1.608	75	1.653
46	1.499	56	1.561	66	1.613	76	1.657
47	1.506	57	1.567	67	1.617	77	1.661
48	1.512	58	1.572	68	1.622	78	1.665
49	1.519	59	1.577	69	1.627	79	1.669

TABLE 4.—*Logarithms of Weight in Pounds*

Log. $\left[\left(\frac{\text{Weight}}{2.20462}\right)^{0.425} \times 71.84\right]$

Pounds	Log.	Pounds	Log.	Pounds	Log.	Pounds	Log.	Pounds	Log.	Pounds	Log.
50	2.433	80	2.520	110	2.578	140	2.623	170	2.659	40	2.392
51	2.436	81	2.522	111	2.580	141	2.624	171	2.660	41	2.396
52	2.440	82	2.524	112	2.582	142	2.625	172	2.661	42	2.401
53	2.444	83	2.527	113	2.586	143	2.627	173	2.662	43	2.405
54	2.447	84	2.529	114	2.585	144	2.585	174	2.663	44	2.409
55	2.451	85	2.531	115	2.587	145	2.639	175	2.664	45	2.413
56	2.454	86	2.533	116	2.588	146	2.631	176	2.665	46	2.417
57	2.457	87	2.535	117	2.590	147	2.632	177	2.666	47	2.421
58	2.460	88	2.537	118	2.591	148	2.634	178	2.667	48	2.425
59	2.464	89	2.539	119	2.593	149	2.635	179	2.668	49	2.428
60	2.467	90	2.541	120	2.594	150	2.636	180	2.668	..	.....
61	2.470	91	2.543	121	2.596	151	2.637	181	2.670	..	.....
62	2.473	92	2.545	122	2.597	152	2.638	182	2.671	..	.....
63	2.476	93	2.547	123	2.599	153	2.639	183	2.672	..	.....
64	2.479	94	2.549	124	2.600	154	2.641	184	2.673	..	.....
65	2.481	95	2.551	125	2.602	155	2.642	185	2.674	..	.....
66	2.484	96	2.553	126	2.603	156	2.643	186	2.675	..	.....
67	2.487	97	2.555	127	2.605	157	2.644	187	2.676	..	.....
68	2.490	98	2.557	128	2.606	158	2.645	188	2.677	..	.....
69	2.493	99	2.559	129	2.608	159	2.646	189	2.678	..	.....
70	2.495	100	2.561	130	2.609	160	2.647	190	2.679	..	.....
71	2.498	101	2.563	131	2.611	161	2.649	191	2.680	..	.....
72	2.500	102	2.564	132	2.612	162	2.650	192	2.681	..	.....
73	2.502	103	2.566	133	2.613	163	2.651	193	2.682	..	.....
74	2.505	104	2.568	134	2.615	164	2.652	194	2.683	..	.....
75	2.508	...	.....	135	2.616	165	2.653	195	2.684	..	.....
76	2.510	105	2.570	136	2.618	166	2.654	196	2.685	..	.....
77	2.513	106	2.572	137	2.619	167	2.655	197	2.686	..	.....
78	2.515	107	2.573	138	2.620	168	2.656	198	2.687	..	.....
79	2.517	108	2.575	139	2.621	169	2.658	199	2.688	..	.....
..	.....	109	2.577	...	.....	...	.....	200	2.689	..	.....

TABLE 5.—*Anti-logarithms for Use in Computing Surface Area*

Log.	0	1	2	3	4	5	6	7	8	9
3.84	6918	6934	6950	6966	6982	6998	7015	7031	7047	7063
3.85	7079	7096	7112	7129	7145	7161	7178	7194	7211	7228
3.86	7244	7261	7278	7295	7311	7328	7345	7362	7379	7396
3.87	7413	7430	7447	7464	7482	7499	7516	7534	7551	7568
3.88	7586	7603	7621	7638	7656	7674	7691	7709	7727	7745
3.89	7762	7780	7798	7816	7834	7852	7870	7889	7907	7925
3.90	7943	7962	7980	7998	8017	8035	8054	8072	8091	8110
3.91	8128	8147	8166	8185	8204	8222	8241	8260	8279	8299
3.92	8318	8337	8356	8375	8395	8414	8433	8453	8472	8492
3.93	8511	8531	8551	8570	8590	8610	8630	8650	8670	8690
3.94	8710	8730	8750	8770	8790	8810	8831	8851	8872	8892
3.95	8913	8933	8954	8974	8995	9016	9036	9057	9078	9099
3.96	9120	9141	9162	9183	9204	9226	9247	9268	9290	9311
3.97	9333	9354	9376	9397	9419	9441	9462	9484	9506	9528
3.98	9550	9572	9594	9616	9638	9661	9683	9705	9727	9750
3.99	9772	9795	9817	9840	9863	9886	9908	9931	9954	9977

TABLE 5.—*Anti-logarithms for Use in Computing Surface Area—Continued*

Log.	0	1	2	3	4	5	6	7	8	9
4.00	10000	10020	10050	10070	10090	10120	10140	10160	10190	10210
4.01	10230	10260	10280	10300	10330	10350	10380	10400	10420	10450
4.02	10470	10500	10520	10540	10570	10590	10620	10640	10670	10690
4.03	10720	10740	10760	10790	10810	10840	10860	10890	10910	10940
4.04	10960	10990	11020	11040	11070	11090	11120	11140	11170	11190
4.05	11220	11250	11270	11300	11320	11350	11380	11400	11430	11460
4.06	11480	11510	11530	11560	11590	11610	11640	11670	11690	11720
4.07	11750	11780	11800	11830	11860	11890	11910	11940	11970	11990
4.08	12020	12050	12080	12110	12130	12160	12190	12220	12250	12270
4.09	12300	12330	12360	12390	12420	12450	12470	12500	12530	12560
4.10	12590	12620	12650	12680	12710	12740	12760	12790	12820	12850
4.11	12880	12910	12940	12970	13000	13030	13060	13090	13120	13150
4.12	13180	13210	13240	13270	13300	13340	13370	13400	13430	13460
4.13	13490	13520	13550	13580	13610	13650	13680	13710	13740	13770
4.14	13800	13840	13870	13900	13960	13960	14000	14030	14060	14090
4.15	14130	14160	14190	14220	14260	14290	14320	14350	14390	14420
4.16	14450	14490	14520	14550	14590	14620	14660	14690	14720	14760
4.17	14790	14830	14860	14890	14930	14960	15000	15030	15070	15100
4.18	15140	15170	15210	15240	15280	15310	15350	15380	15420	15450
4.19	15490	15520	15560	15600	15630	15670	15700	15740	15780	15810
4.20	15850	15890	15920	15960	16000	16030	16070	16110	16140	16180
4.21	16220	16260	16290	16330	16370	16410	16440	16480	16520	16560
4.22	16600	16630	16670	16710	16750	16790	16830	16870	16900	16940
4.23	16980	17020	17060	17100	17140	17180	17220	17260	17300	17340
4.24	17380	17420	17460	17500	17540	17580	17620	17660	17700	17740
4.25	17780	17820	17860	17910	17950	17990	18030	18070	18110	18160
4.26	18200	18240	18280	18320	18370	18410	18450	18490	18540	18580
4.27	18620	18660	18710	18750	18790	18840	18880	18920	18970	19010
4.28	19050	19100	19140	19190	19230	19280	19320	19360	19410	19450
4.29	19500	19540	19590	19630	19680	19720	19770	19820	19860	19910
4.30	19950	20000	20040	20090	20140	20180	20230	20280	20320	20370
4.31	20420	20460	20510	20560	20610	20650	20700	20750	20800	20840
4.32	20900	20940	20990	21040	21090	21130	21180	21230	21280	21330
4.33	21380	21430	21480	21530	21580	21630	21680	21730	21780	21830
4.34	21880	21930	21980	22030	22080	22130	22180	22230	22280	22340
4.35	22390	22440	22490	22540	22590	22650	22700	22750	22800	22860
4.36	22910	22960	23010	23070	23120	23170	23230	23280	23330	23390
4.37	23440	23500	23550	23600	23660	23710	23770	23820	23880	23930
4.38	23990	24040	24100	24150	24210	24270	24320	24380	24430	24490
4.39	24550	24600	24660	24720	24770	24830	24890	24950	25000	25060
4.40	25120	25180	25230	25290	25350	25410	25470	25530	25590	25640
4.41	25700	25760	25830	25880	25940	26000	26060	26120	26180	26240

THE INTRADERMAL SALT SOLUTION TEST IN NEPHRITIS IN ADULTS *

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In previous contributions from the Otho S. A. Sprague Memorial Institute, McClure and Aldrich [1] reported work which demonstrated that the elevation [2] made by intradermal injection of physiologic sodium chloride becomes impalpable more quickly in edematous and pre-edematous states than in the normal condition. Their reports dealt principally with edema associated with disturbances of the kidney in children, but also included several cases of cardiac disease and anemia.

Their studies of the edema with associated renal disturbance led them to favor the hypothesis that the edema in the type of case described is due to an intoxication of the tissues which causes them to take up and to hold more water than normally. They found the test of considerable value in indicating the prognosis in these cases.

Subsequently Baker [3] used the test in the study of scarlet fever and diphtheria, and found it useful in indicating improvement or aggravation of these conditions.

Harrison [4] found a shortening of the time required for the disappearance of the wheal raised in the intradermal salt solution test in cases of lobar pneumonia in children, followed by a gradual return to normal after the crisis. Olmsted [5] applied the test to the study of

* From the Otho S. A. Sprague Memorial Institute and the Pathological Laboratory of the Cook County Hospital.

1. McClure, W. B., and Aldrich, C. A.: Time Required for Disappearance of Intradermally Injected Salt Solution, J. A. M. A. **81**:293 (July 28) 1923. McClure, W. B., and Aldrich, C. A.: Intradermal Salt Solution Test; Its Prognostic Value in "Nephritis" with Generalized Edema, J. A. M. A. **82**:1425 (May 3) 1924.

2. In the test as described by McClure and Aldrich, 0.2 cc. of a sterile 0.8 per cent aqueous solution of sodium chloride is injected intracutaneously under aseptic precautions in two places about 2 cm. apart in the flexor surface of the forearm, and also usually either in the inner surface of the calf or the lateral aspect of the anterior surface of the leg. The time that the elevation remains palpable is noted. For normal children over 1 year of age, the time is one hour or longer. For white adults, the normal time seems to be somewhat higher than in children, and still higher in negro adults (Lash, A. F.: Surg. Gynec. Obst. **43**:40, 1926).

3. Baker, W. J.: Intradermal Salt Solution Test in Scarlet Fever and Diphtheria Patients, J. A. M. A. **83**:1566 (Nov. 15) 1924.

4. Harrison, J.: Intradermal Salt Solution Test in Lobar Pneumonia in Children, J. A. M. A. **84**:1258 (April 25) 1925.

5. Olmsted, H. C.: Intradermal Salt Solution Test in Cardiac Disease in Children, Arch. Int. Med. **37**:281 (Feb.) 1926.

cardiac disease in children. Cohen and his co-workers [6] found a marked decrease in the time of the wheal disappearance in the extremities, in the presence of a vascular pathologic condition, and found the test useful in determining the level of adequate circulation in planning for surgical intervention. Kunde [7] extended the study of the test to a series of adult patients with different forms of nephritis, typhoid fever, toxemias of pregnancy and other conditions, and attempted to correlate the observations with regard to the time necessary for the disappearance of the wheal with the observations made with the elastometer and those made on the urine and on the blood. Lash [8] made use of this test in the study of the toxemias of pregnancy, and found a close relationship between the degree of severity of the toxemia and the amount of lowering of the disappearance time. Guggenheimer and Hirsch [9] studied edema with the aid of this test and obtained results similar to those of McClure and Aldrich and others. They offer, however, a mechanical hypothesis to explain the rapid absorption of salt solution by edematous tissues.

INTRADERMAL SALT SOLUTION TEST IN NEPHRITIS IN ADULTS

The study of the test in nephritis in adults is made difficult by the scarcity of uncomplicated cases, the uncertainty of the clinical determination of their type and the extent to which cardiac and vascular disturbances play a part in their symptoms.

In our series of cases, with a clinical diagnosis of some form of nephritis, there were patients with and without edema.

The basic observation of McClure and Aldrich that the elevation produced by the intradermal injection of physiologic sodium chloride solution disappears rapidly in edematous areas has been found to be true.

A short disappearance time was also found in some cases in which there was no palpable edema, which was in accordance with the observations of McClure and Aldrich who had found the time shortened in edematous patients in areas of skin in which palpable edema was absent.

The observations in the cases studied by us are summarized in the accompanying table.

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6. Cohen, M. B.: Intracutaneous Salt Solution Test; Preliminary Report of Simple Method for Deficiency of Circulation in Extremities, J. A. M. A. **84**: 1561 (May 23) 1925. Cohen, M. B.; Applebaum, H. S., and Hainsworth, E. L.: Intracutaneous Salt Solution Test; Its Use as Test of Efficiency of Circulation in Extremities, J. A. M. A. **86**:1677 (May 29) 1926. Cohen, M. B., and Stern, W. G.: Intracutaneous Salt Solution Wheal Test; Its Value in Disturbances of Circulation in Extremities, J. A. M. A. **87**:1355 (Oct. 23) 1926.

7. Kunde, M. M.: Edema; Correlation of Elastometer Findings, Disappearance Time for Intradermally Injected Salt Solution, Urinalysis and Nitrogen Retention of Blood in Edema, Arch. Int. Med. **38**:57 (July) 1926.

8. Lash, A. F.: Surg. Gynec. Obst. **43**:40, 1926.

9. Guggenheimer, H., and Hirsch, P.: Klin. Wchnschr. **5**:704, 1926.

Results of Intradermal Salt Solution Test on Eighteen Patients, Seventeen of Whom Were Suffering from Nephritis

Case Sex Race Age	Diagnosis	Date of Tests	Disappearance Time in Minutes: Forearm	Disappearance Time in Minutes: Leg	Palpable Edema in: Forearm	Palpable Edema in: Leg	Urinary Observations: Albumin	Urinary Observations: Red Blood Cells	Urinary Observations: White Blood Cells	Urinary Observations: Casts	Blood Chemistry: Total Nonprotein Nitrogen, Mg. per 100 Cc. Blood	Blood Chemistry: Urea Nitrogen, Mg. per 100 Cc. Blood	Blood Chemistry: Creatinine, Mg. per 100 Cc. Blood	Blood Chemistry: Uric Acid, Mg. per 100 Cc. Blood	Blood Chemistry: Sodium Chloride, per Cent	Blood Chemistry: Cholesterol, per Cent	Blood Chemistry: Carbon Dioxide Capacity
1. C. P. male white 41 years	Chronic nephritis	10/ 9/26	..	..	..	..	+++	+									
		10/10/26	..	..	..	..	+	+									
		10/22/26	..	..	..	..	..	..	..	..	128.6	95.7	4.0	8.0			
		10/23/26 (Died)	<1	<1	++++	++++	..	..	..	..	170.0	.....	7.8	10.0	0.58	0.21	
An obese, muscular man complaining of dyspnea of 7 years' duration, edema of the extremities and scrotum of one week's duration. Examination revealed massive edema of the arms, legs, penis, scrotum and abdominal wall. During stay in hospital he became progressively worse, had severe headaches, became irrational and died. Autopsy observations were: chronic glomerulonephritis; generalized anasarca; bilateral pulmonary edema; cerebral edema, early fibrinous pericarditis																	
2. A. Z. male white 54 years	Chronic interstitial nephritis and hypertension	10/16/26	54	40	—	—	+	—	—	—	40.0	.....	8.0	2.0	0.60	0.17	
		11/ 8/26	55	48	—	—	+	—	—	—							
A poorly developed, poorly nourished man complaining of asthenia and generalized pains of 1½ months' duration. Examination revealed puffiness under the eyes but no edema of the extremities. Skin dry and anemic; heart slightly enlarged without murmurs and a regular rhythm; liver 3 cm. below the costal margin; Wassermann test negative; blood pressure: systolic 160, distolic 80; red blood cells, 2,190,000; white blood cells, 5,600; hemoglobin, 40 per cent.; no abnormal blood cells. He did not improve under treatment.																	
3. S. C. male white 42 years	Impending uremia; chronic nephritis with hypertension	10/25/26	..	..	—	—	+++	—	—	—	63.4	42.9	3.0	2.2			
		10/28/26	64	50	—	—	++	—	—	—	67.0	55.0	7.5	2.2	0.48	0.10	
		11/ 4/26	67	60	—	—	+	—	—	—	55.0	33.0	7.5	2.0	0.48	0.14	
		11/11/26	54	43	—	—	+	—	—	—							
A well nourished, rather flabby man, admitted in a semicomatose, incoherent condition. Physical examination was essentially negative; blood pressure on admittance: systolic 220, diastolic 150; Wassermann test negative; red blood cells, 6,490,000; white blood cells, 21,900; hemoglobin, 100 per cent. He rapidly improved. On becoming rational had a marked speech defect and impairment of vision, both of which disappeared with convalescence. Blood pressure on discharge: systolic 160, diastolic 110																	
4. J. C. female colored 28 years	Chronic nephritis with uremia; pulmonary tuberculosis; fibrinous pericarditis; arteriosclerosis	10/28/26	..	..	—	—	++++	—	—	—	176.0	143.0	5.0	9.2			
		11/ 1/26	75	58	—	—	++	—	—	—	193.0	.....	10.5	10.0	0.54		
		11/ 9/26	50	43	—	—	++	—	—	—	211.0	176.4	8.9	15.0			
		11/15/26	45	40	—	—	+++	—	—	—	215.0	.....	7.0	16.0			
		11/18/26	40	33	—	—	+++	—	—	—	322.0	172.0	9.0	12.0	0.60	0.13	
A slender emaciated woman, dyspneic, complaining of cough, headache, tinnitus, hemoptysis of 9 months' duration; epistaxis, vomiting of 2 weeks' duration. Physical examination revealed an enlarged heart with a systolic murmur heard at the apex; lungs impaired, apical resonance with inspiratory crackles and moist râles in them; no edema. She was at all times mentally acute and remained about in the same condition while in the hospital. Wassermann test negative; blood pressure: systolic 200, diastolic 120; red blood cells, 2,600,000; white blood cells, 11,600; hemoglobin, 40 per cent																	
5. K. L. female white 45 years	Chronic interstitial nephritis with hypertension	11/ 8/26	45	30	±	±	++	—	—	—	57.3	.....	....	3.0			
		11/10/26	41	32	—	—	++	—	—	—							
		11/12/26	48	33	—	—	++	—	—	—	52.0	.....	....	2.3			
		11/22/26	52	38	—	—	++	—	—	—	40.9	20.3					
A rather obese woman not acutely ill, complaining of intermittent swelling of the ankles, anorexia, headaches, and pain in the right lumbar region. Physical examination was essentially negative; Wassermann test negative; blood pressure: systolic 140, diastolic 110; white blood cells, 10,800. Uneventful improvement																	

6. C. A. male colored 37 years	Generalized arteriosclerosis; chronic nephritis; syphilitic aortitis; aortic insufficiency	11/17/26 11/23/26 11/30/26	93 77 89	74 75 83	— — —	— — —	+++ +++ +++	— — —	— — —	— — —	43.0	33.0	3.2	2.1	0.45	0.23	

A heavily musceled man complaining of headaches, dizzy spells, dyspnea, and frequency of urination, all of 1 month's duration. Physical examination revealed cardiac disease; blood pressure: systolic 170, diastolic 100; Wassermann test positive; red blood cells, 3,530,000; white blood cells, 11,000; hemoglobin, 80 per cent. Was relieved of his symptoms during stay in hospital; blood pressure and urine remained unchanged

7. S. T. female white 68 years	Chronic parenchymatous nephritis; hydrothorax; ascites; vesicovaginal fistula	11/10/26 11/16/26 11/18/26 11/21/26 12/10/26	.. 15 11 5 <1	.. 12 12 5 <1	.. ++ ++ +++ +++	.. ++ +++ +++ +++	.. ++ +++ +++ +++	.. — — — —	.. — — — —	.. — — — —	68.8 95.0 72.0 	47.2 58.0 	3.3 6.0 3.0 	2.8 4.0 3.3 	 0.56 	 0.35 	

A rather obese, flabby woman complaining of swelling of the ankles, incontinence of urine and burning on urination. Physical examination revealed marked edema of the extremities, shifting abdominal dulness, edema about the face and of the abdominal wall; dulness over both pulmonary bases, breath sounds feeble; heart enlarged to the left; Wassermann test positive; blood pressure: systolic 170, diastolic 100. Treatment with digitalis and causing the patient to perspire resulted in temporary improvement; then became progressively worse until death

8. B. D. female colored 31 years	Chronic glomerulotubular nephritis; diphtheritic ulcers of sigmoid; hydrothorax; hydroperitoneum; cardiac hypertrophy	11/ 8/26 11/ 9/26 11/10/26 11/13/26 11/15/26 11/16/26 (died)	.. .. .. 30 20	.. .. .. 33 18	.. .. + + +	.. .. ++ ++ ++	++ ++ ++ ++ ++	— — — — —	— — — — —	— — — — —	212.0	177.0 137.4	8.5	18.0 12.5	 	 	

A well developed, moderately emaciated woman complaining of dyspnea, orthopnea, swelling of the ankles, asthenia, nausea and vomiting of 2 months' duration. Physical examination revealed moderate edema of the extremities; an enlarged, tender liver; hydrothorax and a transversely enlarged heart. Patient had frequent attacks of vomiting; increasing dyspnea, and weakness and a rapidly diminishing mental acuity preceded death; a uremic frost was present on the day before death. The Wassermann test was negative; blood pressure: systolic 180, diastolic 125; red blood cells, 2,050,000; white blood cells, 12,600; hemoglobin, 40 per cent

9. A. G. male white 48 years	Acute parenchymatous nephritis (nephrosis?)	11/18/23 11/20/26 11/23/26 11/30/26 12/10/26 12/15/26 (died)	4 3 {R 1 {L 1 {R <1 {L 15 {R <1 {L 21	4 3 1 <1 <1 	+++ +++ {R +++ {L ++ {R +++ {L + {R +++ {L —	+++ +++ +++ +++ +++ 	++ +++ +++ +++ +++ 	— — — — — 	— — — — — 	— — — — — 	.... 63.0 	..... 35.0 46.0 	.... 5.0 	5.0 2.0 	 0.52 	 0.120 	

Dyspnea of 2 months' duration, and swelling of the extremities and trunk of 1 week's duration. Physical examination revealed marked edema of arms, legs, face, trunk and genitalia; ascites; a few moist râles over the right chest. Patient's condition remained about the same until death, with the exception of the gradual disappearance of edema in the left arm. The two arms showed a marked difference in the time of disappearance of the wheal.

10. P. H. male white 44 years	Acute nephritis	1/21/27 1/22/27 1/21/27 1/25/27	60 60 80 70	85° 50 75 65	— — — —	+ + + +	+++ +++ +++ +++	.. ..	++ ++ ++ ++	+ + + +	150.0 	100.0 	3.3 	8.0 	0.54 	0.286 	33.0

An obese, muscular man, presumably well up to three weeks before admission. Complaint: shortness of breath, cough, hemoptysis, hoarseness, edema of ankles, all following a cold three weeks previously. Not much change in edema during the ten days spent in hospital. Blood pressure: systolic 170, diastolic 80; Wassermann test negative. Patient died Jan. 27, 1927. There was pitting edema both in the thigh and leg, but none in the knee region, which was used in the tests on the leg

Results of Intradermal Salt Solution Test on Eighteen Patients, Seventeen of Whom were Suffering from Nephritis—Continued

Case Sex Race Age	Diagnosis	Date of Tests	Disappearance Time in Minutes: Forearm	Disappearance Time in Minutes: Leg	Palpable Edema in: Forearm	Palpable Edema in: Leg	Urinary Observations: Albumin	Urinary Observations: Red Blood Cells	Urinary Observations: White Blood Cells	Urinary Observations: Casts	Blood Chemistry: Total Nonprotein Nitrogen, Mg. per 100 Cc. Blood	Blood Chemistry: Urea Nitrogen, Mg. per 100 Cc. Blood	Blood Chemistry: Creatinine, Mg. per 100 Cc. Blood	Blood Chemistry: Uric Acid, Mg. per 100 Cc. Blood	Blood Chemistry: Sodium Chloride, per Cent	Blood Chemistry: Cholesterol, per Cent	Blood Chemistry: Carbon Dioxide Capacity
11. F. S. male white 35 years	Chronic nephritis	2/11/27	..	..	..	..	..	..	..	..	75.0	53.2	4.0				
		3/15/27	12	12	—	—	+	..	..	+							
		3/16/27	12	12	—	—	..	..	..	..	275.0	187.0	12.0	11.0	0.51	0.267	21.1
		3/17/27	12-14	12-14	—	—											
		3/18/27	14	11-12	—	—											
A rather thin person. He gave a history of a cold, followed eight days later by dysuria, small urinary output, swelling of ankles and shortness of breath on exertion. Phenolsulphonphthalein test, 4 per cent output in 2 hours; blood pressure: systolic 182, diastolic 100 on Feb. 2, 1927; Wassermann test, negative. Feb. 11, 1927: hemoglobin, 80 per cent; red blood cells, 2,640,000; white blood cells, 6,800. March 7, 1927: hemoglobin, 50 per cent; red blood cells, 1,800,000. Patient was on digitalis treatment from Feb. 11, 1927, to March 18, 1927, the day of his death. Edema not present in the extremities during the time the tests were carried out																
12. V. S. male white 42 years	Nephritis with hypertension; pericarditis with effusion	2/26/27	..	..	..	..	..	..	..	..	.....	125.5					
		3/15/27	¾	¾	++	++	+	..	..	+	906.0	150.0	9.0	12.0	0.53	0.173	45.7
A dyspneic, edematous person in great distress. It was the last day of his life. Complaint: swelling of ankles, shortness of breath, dimness of vision, frequency with small amounts of urine, all of 3 weeks' duration. Physical observations: generalized edema, cyanotic lips, enlarged liver and heart, pericardial rub over lower sternum; blood pressure, systolic 190, diastolic 114 on Feb. 26, 1927; hemoglobin, 85 per cent; red blood cells, 2,930,000; white cells, 6,100																	
13. W. U. male colored 43 years	Chronic glomerulo nephritis	3/16/27	..	..	..	..	..	..	..	..	83.0	.....	4.6	5.0	....	.....	52.0
		3/17/27	60	50	—	—	++	++	..	+							
		3/19/27	45	38	—	—	++	++	..	+							
		3/21/27	36	35	—	—	++	++	..	+	150.0	125.0	7.5	10.0	0.41	0.210	93.0
		3/22/27	35-40	20	—	—	++	++	..	+							
		3/23/27	35	25	—	—	++	++	..	+							
		3/24/27	35	35	—	—	++	++	..	+							
		3/28/27	10	10	—	—	++	++	..	+							
		3/29/27	3	10	—	—	++	++	..	+	182.0	131.0	11.4	13.3	0.35	0.270	96.0
		3/30/27	3-4	7	—	—	++	++	..	+							
		3/31/27	2	3	—	—	++	++	..	+	250.0	154.0	16.0	18.0	0.37	.....	94.0
		4/ 1/27	3	3	—	—	++	++	..	+							
		4/ 2/27	8	12-14	—	—	++	++	..	+	.....	.....	....	....	....	.....	82.6
A muscular colored man giving a history of headaches, dizzy spells, hiccuping, dyspnea on exertion, dimness of vision, occasional tinnitus, etc., leading to a diagnosis of nephritis with hypertension. There was never edema of the extremities, neither before nor during his stay at the hospital. Blood pressure: systolic 270, diastolic 165 on March 14, 1927. The patient was receiving 3 drachms (11.655 Gm.) of powdered sodium bicarbonate a day between March 14, 1927, and April 1, 1927, and developed an alkalosis as can be seen from the blood chemistry data. Clinically the alkalosis manifested itself by continuous clonic twitching of the musculature, wild, staring look and a temporary psychosis. All of these subsided considerably when bicarbonate was discontinued and replaced by sodium acid phosphate three days before his death. The last determination of the carbon dioxide capacity was carried out one day before he died, after two days of treatment with sodium acid phosphate																

14. A. A. male white 46 years	Chronic parenchymatous nephritis	3/18/27	14	4	++	++	++	+	+	+	.....	36.0	2.3	....	....	....	54.0
		3/19/27	38	3-4	—	++											
		3/22/27	50	45	—	±	..	..	..	..	33.0	21.0	2.0	8.5	0.54	0.210	64.0
		3/26/27	65	65	—	—											

A well developed person, complaining of generalized swelling of 5 weeks' duration, severe nose bleeds and morning headaches of several days' duration. The heart was normal. The edema rapidly subsided after rest in bed and diuretin treatment. Phenolsulphonphthalein test, 40 per cent output in 2 hours; blood pressure: systolic 160, diastolic 70 on March 18, 1927; Wassermann test, negative; urinalysis negative for albumin after March 28, 1927

15. M. F. male colored 39 years	Chronic nephritis with hypertension; etiology: scarlet fever 4 years ago	4/14/27	65	20-25	—	—	+++	+	+	..	130.0	.....	14.0	7.5			
		4/15/27	70	17	—	—											
		4/16/27	..	..	..	..	..	..	..	..	142.0	.....	18.0	11.0			
		4/20/27	..	..	..	..	..	..	..	..	166.0						
		4/21/27	35	15	—	—											
		4/22/27	35	18	—	—					276.0	174.0	16.0	12.0	0.47	....	39.0
		4/25/27 10 a.m.	32	8-10	—	—	..	..	..	..	440.0	.....	12.0	13.3	0.45	....	20.2
		4/25/27 4 p.m.	16-18	10	—	—											

A well developed colored man, complaining of abdominal pain, vomiting, dizzy spells and blurring of vision, all of short duration. Scarlet fever four years previously and swollen for two weeks after fever subsided; since then nocturia 4 or 5 times a night. Edema was not present; Wassermann test, negative; blood pressure: systolic 240, diastolic 180 on April 13, 1927. Rest in bed, limited diet of milk and water, and magnesium sulphate in the morning constituted the treatment. Died three hours after the last test, having taken a sudden bad turn that afternoon

16. C. H. male colored 44 years	Chronic nephritis with hypertension	3/31/27	..	..	..	..	..	..	..	..	42.0	21.5	1.8	3.9			
		4/15/27	25	25	—	—	++	..	+								
		4/16/27	..	..	..	..	..	..	..	..	71.0	.....	2.1	3.0			
		4/17/27	65	10	—	—	..	..	..	..	100.0	58.0	4.0	6.2	0.50	0.120	75.8

A well developed colored man, complaining of shortness of breath, cough, headaches, malaise, epigastric pain and swelling of ankles. Physicial examination revealed enlarged heart and liver and markedly sclerosed vessels. Slight edema on admission, but none during the time the tests were carried out. Blood pressure: systolic 190, diastolic 150 on March 27, 1927; Wassermann test negative. Discharged April 4, 1927, improved

17. J. I. male white 38 years	Poisoning with mercuric chloride	3/19/27	..	..	..	..	++	++	++	+	100.0	75.0	7.1				
		3/21/27	35	40	—	—	++	++	++	+							
		3/22/27	30	30	—	—	++	++	++	+							
		3/25/27	35	35	—	—	++	++	++	+	118.0	88.6	9.0	7.0			
		3/25/27	30	30	—	—	++	++	++	+	250.0	150.0	15.0	12.8	0.49	0.185	31.0

Stated that he swallowed 8 tablets of mercuric chloride, 7½ grains (4.9 Gm.) each. He vomited a quantity of green material ten minutes later. Brought to the hospital an hour and a half later in shock and with a rapid, weak pulse. Suppression of urinary output from the beginning. Wassermann test negative. Died March 27, 1927 after ten days in hospital. Ascending paralysis preceded death

18. A. O. male white 40 years	Acute nephritis; etiology; arsenical and mercurial treatment for syphilis	5/ 2/27	..	..	..	..	++	..	+	+	.....	30.0	2.0	3.3			
		5/12/27	20	0.5	—	++	++	..	+	+							
		5/16/27	30	1	—	+	++	..	+	+							
		5/17/27	18	0.5	—	++	++	..	+	+							
		5/19/27	25	1	—	++	++	..	+	+							
		5/23/27	20	0.5	—	++	++	..	+	+	.....	39.0					
		5/26/27	17	0.5	—	++	++	..	+	+							
		6/ 3/27	5	0.5	+	++	++	..	+	+	54.0	31.5	2.1	4.0	0.478	0.285	58.4
		6/ 5/27 (died)															

A rather slim person complaining of swelling of both legs, scrotum, penis and abdomen, all of one week's duration. Edema was not present in the arms on admission; had a chancre in September, 1925, and received intensive antisyphilitic treatment since that time; blood pressure: systolic 118, diastolic 70; Wassermann test negative; hemoglobin, 90 per cent; red blood cells, 4,320,000; white blood cells, 10,600. Put on a limited protein diet, restricted fluids. Magnesium sulphate and special alkalis (mixture of sodium bicarbonate, sodium acetate and sodium citrate, 1 Gm. of each, three times a day). Considerable diarrhea set in and the edema subsided somewhat. Pain, which was extremely marked in the right extremity on admission, disappeared. On May 17, the edema began getting worse, affecting the back of chest. On June 3, there was marked edema of the forearm and back of chest. On June 4, motor paralysis of right extremity developed; an extreme tenderness to touch in all edematous areas. Patient died on June 5, 1927.

INDIVIDUAL CASES

In cases 1 and 12, the patients had an extreme degree of anasarca. The results were as expected—an extremely short disappearance time, less than one minute; in fact, it was practically impossible to raise a wheal by the injection of salt solution. Both patients were moribund.

In cases 2, 3, 4, 5 and 6, cases of nephritis without edema, the disappearance time was not much shortened either in the arm or in the leg, but was usually somewhat longer in the arm. In case 7, the amount of edema was about equal in the arm and in the leg, and the disappearance time was approximately the same.

In case 8 the patient had nephritis with a mild degree of edema, and there was considerable decrease in the disappearance time. This case resembles case 4 in many respects; in both the retention of nitrogen and the blood pressure were high; they differ in that there was an absence of edema in case 4, which caused a marked difference in the disappearance time in the two cases. In both patients the disappearance time decreased as they became clinically worse, although evident change in the degree of edema did not occur.

In case 9, on admission to the hospital, the patient had marked edema in both the upper and lower extremities, and the disappearance time was correspondingly short. Later the edema of the left forearm subsided somewhat, and this was associated with an increase in the disappearance time.

In case 10, a case of acute nephritis, there was palpable edema of both legs, which was less in the thighs and absent in the region of the knee and in the arms. The disappearance time was long both in the forearm and in the knee region. Unfortunately, in this case the test was not carried out in the region of the calf when palpable edema was present. As permission for necropsy was not obtained, it is difficult to rule out cardiac edema.

In case 11 we were dealing with chronic nephritis in a comparatively young person. Although there was no palpable edema during the time that the salt solution tests were carried out, the disappearance time in both the arm and the leg was remarkably short and approximately constant. Both the present study and the results obtained by Kunde [7] seem to show that there is no relationship between the short disappearance time and the high degree of retention of nitrogen. The relationship to the low carbon dioxide capacity of the blood is suggestive but not certain, because the analysis was carried out only one day before the patient's death.

In case 13, the patient gave a typical history leading to a clinical diagnosis of chronic nephritis with hypertension. On postmortem examination, chronic glomerulonephritis, marked concentric hypertrophy of the heart and moderate atheromatous degeneration of the aortic,

tricuspid and mitral leaflets were found. The patient spent about three weeks in the hospital, during which time there was no palpable edema. The disappearance time in both the arm and the leg was within normal limits soon after admission, but, as seen from the results in the table, there was a steady decline with a sharp break about two weeks after the patient was admitted. The patient had been placed on a treatment with sodium bicarbonate (1 drachm [3.885 Gm.] three times a day) on the day of admission to the hospital, but this was discontinued three days before the patient's death. As is seen from the results of a chemical examination of the blood made seven days after admission to the hospital, the patient was in a state of alkalosis. Nearly a week later, a sudden diminution occurred in the disappearance time. At the same time, the patient began to show marked symptoms of nervousness and continuous intense clonic twitchings of the musculature, which was especially pronounced in the extremities. In the next few days the disappearance time fell still lower, to two and three minutes in the forearm and leg, respectively. At the same time, while the degree of nitrogen retention was constantly increasing, the carbon dioxide capacity remained at the same high level. The patient, meanwhile, complained of great thirst, the twitchings continued, and he apparently developed a psychosis. Such was his condition three days before his death, when the administration of sodium bicarbonate was stopped and sodium acid phosphate was substituted. Two days later, the twitching of his muscles subsided and his mind cleared up considerably; at the same time the disappearance time rose somewhat and the carbon dioxide capacity fell to 82.6. As the patient died the day following the last test, one can only speculate whether the disappearance time would have increased much more on continued treatment with the acid salt.

In case 14, the patient came to the hospital with generalized edema, especially marked in the lower extremities. Cardiac symptoms were not observed, and the symptoms were thought to be caused by an acute exacerbation of chronic parenchymatous nephritis. The edema quickly subsided on treatment with diuretin, and with it the disappearance time of the salt solution was increased. The disappearance time both in the arm and the leg was normal in less than a week after treatment was started.

In case 15, the patient's symptoms led to a diagnosis of nephritis with hypertension. He had had scarlet fever four years previously, and had been edematous for about two weeks afterward. On admission to the hospital, there was no palable edema, and the disappearance time was normal in the arm but was low in the leg. The disappearance time in the leg remained at about the same level during the twelve days the patient spent at the hospital, but became still shorter on the last day of the

patient's life. The disappearance time in the arm dropped to the low level of from sixteen to eighteen minutes in the last afternoon, when there was a sudden rapid change for the worse, and he died a few hours later. What the relation was between the low carbon dioxide capacity of the blood and the drop in the disappearance time in the forearm in the last few hours is merely to be surmised. The low disappearance time in the leg is perhaps explainable by circulatory changes.

The patient whose condition is reported in case 16 gave a typical history of nephritis, and the physical observations were that he was suffering from chronic nephritis with hypertension. His heart and liver were enlarged; there were marked sclerotic changes in the vessels and a hemorrhagic exudative neuroretinitis. He had had swelling of the ankles for the nine months previous to admission, but there was no edema during the time these tests were carried out.

The disappearance time in the leg was low while the patient was in the hospital; whether or not this was due to circulatory disturbances cannot be told with certainty.

The patient discussed in case 17 swallowed 60 grains (3.90 Gm.) of mercuric chloride in an attempt to commit suicide. Urinary suppression immediately followed; the degree of retention of nitrogen constantly increased, but the time of disappearance of the salt solution remained unchanged at from thirty to forty minutes.

In case 18, the patient gave a definite history of syphilis and intense antisyphilitic treatment. On admission, there was marked edema of the lower half of the body, but there was no palpable edema in the upper extremities. The time required for the disappearance of wheal was very short in the legs (one-half minute) and moderately short (twenty minutes) in the arms. Attempted treatment was of no avail, and the edema extended to the forearm in the last days of the patient's life, when the disappearance time dropped accordingly. As indicated by the results given in the table, the degree of retention of nitrogen at the end of the patient's life was not much greater than on admission.

COMMENT

The cases of nephritis presented here are insufficient in number to permit the drawing of sweeping conclusions, although they present a few interesting points.

As stated before, the fundamental fact of the rapid disappearance of the elevation made by the intradermal injection of physiologic sodium chloride solution in nephritic edemas, is again confirmed by these studies. The disappearance time in any particular case usually varies during the course of the disease with the changes in the degree of the edema; a persistently low disappearance time usually indicates a bad prognosis.

There is no close relationship apparent between the degree of the edema and the disappearance time, on the one hand, and the retention of nitrogen and the content of sodium chloride and cholesterol in the blood, on the other.

The disappearance time may also be short in cases of nephritis without palpable edema; here, too, no relationship is seen between this short disappearance time and the observations made on the blood during chemical examination. There may, however, be a relationship between the carbon dioxide capacity of the blood and tissues and the disappearance time of the wheal—either a prolonged acidosis or alkalosis leading to a diminished disappearance time.

The influence of the carbon dioxide capacity deserves further study. The examples of a short disappearance time of the wheal in cases of nephritis, in which either acidosis or alkalosis developed in the course of treatment, are rather suggestive, but not conclusive.

In nephritis associated with arteriosclerosis, the circulatory factor must be taken into consideration, especially in interpreting the low results frequently obtained in the region of the leg. In this connection, the work of Cohen and his co-workers, to which reference has been made, is suggestive.

In the case of mercuric chloride poisoning reported in this article, there seemed to be no relationship between the time of the disappearance of the wheal, the urinary output, which was low at all times, and the retention of nitrogen, which was constantly progressing.

SUMMARY

A study of the intradermal salt solution test was made in eighteen cases of nephritis in adults with the following results:

1. The wheals caused by the salt solution disappeared in less than thirty minutes, except in one case (case 13, alkalosis), only when edema or a history of edema was present.

2. A decreasing disappearance time was associated with an unfavorable course of the condition; an increasing disappearance time with improvement; a very short disappearance time, which persisted in spite of treatment, was of bad prognostic significance.

3. There was no close relationship between the retention of nitrogen and the sodium chloride and cholesterol content of the blood, on the one hand, and the disappearance time on the other.

4. In cases in which the carbon dioxide capacity was determined, and evidence of either severe acidosis or alkalosis was found, there was also a marked shortening of the disappearance time, even in the absence of palpable edema. More examples of these types should be examined.

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3. There was no close relationship between the retention of nitrogen and the sodium chloride and cholesterol content of the blood, on the one hand, and the disappearance time on the other.

4. In cases in which the carbon dioxide capacity was determined, and evidence of either severe acidosis or alkalosis was found, there was also a marked shortening of the disappearance time, even in the absence of palpable edema. More examples of these types should be examined.

INTESTINAL ABSORPTION

A SEARCH FOR A LOW RESIDUE DIET *

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There are many occasions when physicians or surgeons wish to use a diet with the least possible residue, particularly in the treatment of patients with diarrhea and following operations about the rectum or anus. If the fecal residues can be made small enough, and if defecation can be postponed for a week or more, not only will the patient be spared much distress, but healing wounds can be kept clean. Considering the importance of this problem, it is surprising to find practically no mention of it in most of the well known textbooks on dietetics.

According to Prausnitz,[1] Bischoff and Voit,[2] Müller,[3] and Rubner,[4] so long as the foods given are completely utilized, the amount of feces voided will remain about the same with different diets. As is well known, a considerable portion of the fecal material is made up of dead bacteria and intestinal secretions; so, even during starvation, a certain amount of feces will always be formed. As one would expect, the bulk of the stools depends largely on the amount of cellulose contained in the food.

Cannon [5] gave cats various foods mixed with bismuth and watched the progress of the material through the bowel. He concluded that proteins pass through the small intestine slowly, fats a little faster and carbohydrates fastest of all. Doubtless these differences were due partly to the varying rates with which these foods pass through the pylorus, but Cannon felt that they were due also to differences in

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1. Prausnitz, Wilhelm: Ueber die Ausnützung der Kuhmilch im menschlichen Darmkanal, Ztschr. f. Biol. **25**:533, 1889; Die Ausnützung der Bohner im Darmkanale des Menschen, ibid. **26**:227, 1890; Die chemische Zusammensetzung des Kothes bei verschiedenartiger Ernährung, ibid. **35**:335, 1897.

2. Bischoff, E., and Voit, quoted by Rubner: Ztschr. f. Biol. **15**:115, 1879.

3. Müller, Friedrich: Ueber den normalen Koth des Fleischfressers, Ztschr. f. Biol. **20**:327, 1884.

4. Rubner, Max: Ueber die Ausnützung einiger Nahrungsmittel im Darmcanale des Menschen, Ztschr. f. Biol. **15**:115, 1879.

5. Cannon, W. B.: The Mechanical Factors of Digestion, London, Edward Arnold, 1911, 227 pp.

the muscular response of the bowel. The rate of passage through the small intestine is important because it may be a factor in determining the amount of digestion and absorption with any one meal.

One of the best articles on the subject of absorption in the small intestine is by Heile,[6] who gave a number of foods to dogs with a cecal fistula. He also studied a few patients with fistulas in the terminal ileum. With dogs on a mixed diet, undigested material began to appear at the fistula at the end of an hour; the greatest amount came through in the third and fourth hours, and by the fifth hour the bowel was clean. With lean meat, the observations were the same. With carbohydrates and fats, the extrusion began sooner; it increased rapidly and ceased after three or four hours.

Heile noticed that milk gave rise to large amounts of residue; when 126 Gm. of well chopped meat was given to a dog, only 20 Gm. of material came away, but when a liter of milk was given containing 130 Gm. of solid material, the residue appearing at the fistula amounted to 250 Gm. Heile was impressed with the desirability of giving proteins when the colon is to be spared work. He found that when from 250 to 500 Gm. of horse flesh was given to a dog, all but 2 per cent was absorbed. When he gave 75 Gm. of sucrose to a dog weighing 11 Kg., it was all absorbed, but when he gave more than 100 Gm., small amounts of reducing material began to come away. One hundred grams of rice was completely absorbed.

In extensive studies of the stools of dogs, Müller showed that when the animals are not given anything but meat or meat and a little sugar, the stools differ little from those obtained during periods of fasting.

According to Babkin,[7] Berlatzki, working with dogs with a cecal fistula, confirmed the observation of others that the giving of milk results in the prompt passage of large amounts of residue. He found that this occurred also when milk was added to foods which otherwise would have been well digested. Another substance that behaved peculiarly was raw egg albumin. The list taken from Babkin's book gives an idea of the results obtained by Berlatzki (table 1).

Babkin and Strashesko thought that it was the lactose in the milk that increased intestinal peristalsis and caused the retention of fluid within the lumen of the bowel. Harley and Goodbody, quoted by Cammidge,[8] also comment on the tendency of milk to increase the bulk of fecal residues.

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6. Heile, B.: Experimentelle Beobachtungen über die Resorption im Dunn- und Dickdarm, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **14**:474, 1905

7. Babkin, B. P.: Die aüssere Sekretion der Verdauungsdrusen, Berlin, Julius Springer, 1914, p. 386.

8. Cammidge, P. J.: The Feces of Children and Adults, Bristol, John Wright & Sons, 1914, p. 317.

Rubner, in his classic article, gives the list of foods which he fed to young healthy men (table 2). It will be seen that the foods that were best used were meat, eggs, rice, white bread, noodles and macaroni. Less well digested were milk, cheese, fats and potatoes. The highest

TABLE 1.—*Results Obtained by Berlatzki with Various Kinds of Food (From Babkin)*

Kind of Food	Amount Collected After Ten Hours, Cc.	Per Cent Excreted
600 cc. water	9.7	1.6
400 Gm. meat	20.8	5.0
200 Gm. bread	34.3	17.1
600 cc. oatmeal (water)	8.0	1.3
600 cc. oatmeal plus milk	253.5	42.2
600 cc. rice plus milk	324.5	54.0
600 cc. mush plus milk	244.0	40.6
600 cc. milk	171.1	28.5
600 cc. skimmed milk	224.7	37.5
600 Gm. curds	25.6	4.3
100 Gm. butter	4.7	4.7
100 cc. olive oil	4.0	4.0
300 Gm. raw egg albumin	79.5	26.5
300 Gm. boiled egg albumin	23.5	7.8
300 Gm. raw egg-yolk	17.5	5.8

TABLE 2.—*List of Food Given by Rubner to Young Healthy Men (From Rubner)*

Food	Percentage Lost in the Stools		
	Dry Substance	Nitrogen	Ash
White bread	3.7	18.7	17.3
White bread	5.2	25.7	25.4
Rice	4.1	20.4	15.0
Macaroni	4.3	17.1	24.1
Macaroni	5.7	11.2	22.2
Meat	4.7	2.5	15.0
Meat	5.6	2.8	21.2
Noodles	4.9	20.5	20.9
Egg plus meat	5.1	2.6	18.1
Egg, hard boiled	5.2	2.9	18.4
Milk plus cheese	6.0	3.7	26.1
Milk plus cheese	6.8	2.9	30.7
Milk plus cheese	11.3	4.9	55.7
Corn	6.7	15.5	30.0
Butter, 240 Gm.	6.7	11.3	20.0
Milk	7.8	6.5	48.8
Milk	8.4	7.0	46.8
Milk no. 5	8.4	7.0	46.8
Milk no. 7	9.4	12.0	44.5
Milk no. 6	10.2	7.7	48.2
Lard, 100 Gm.	8.5	12.1	28.5
Lard, 200 Gm.	9.2	14.0	25.1
Potatoes	9.4	32.2	15.8
Cabbage	14.9	18.5	19.3
Black bread	15.0	32.0	36.0
Carrots	20.7	39.0	33.8

percentage of loss was found with certain samples of milk and cheese, with cabbage, black bread and carrots.

If a low residue diet is desired, Cammidge advises the use of small amounts of white bread and butter, white of egg, lean meat and well cooked rice. Carter, Howe and Mason[9] mention the fact that when

9. Carter, H. S.; Howe, P. E., and Mason, H. H.: Nutrition and Clinical Dietetics, Philadelphia, Lea & Febiger, 1921, p. 47.

milk is added to the diet it will cause considerable increase in the fecal output. They think this is due to unabsorbed calcium, phosphorus and perhaps nitrogen.

At St. Mary's Hospital, Rochester, Minn., the low residue diet prescribed by the dietitian, Miss Smith, is made up of strained fruit juices, broth, tea, coffee, sugar, candy made of sugar alone and jello made with strained fruit juices. Such a diet works satisfactorily, and patients easily go for eight days without a bowel movement.

REPORT OF EXPERIMENTS

The animals used in these studies were prepared by the following method: As is well known, it is not easy to make an ileal fistula in a dog and have him live in comfort. The surrounding skin tends to become excoriated, the operative wound becomes infected, and healing is retarded or made impossible To avoid this difficulty, animals were operated on as follows: Under ether anesthesia, the last 25 cm. of ileum was resected together with the colon up to a point 6 cm. from the anus. End to end anastomosis was then performed on the ileum and rectum. In one of the three animals on which our observations were made 10 cm. of the colon had to be left on account of the situation of some large arteries. Animals were thus obtained which to all intents and purposes had a fistula of the terminal ileum, but which were much easier to take care of because they possessed a normal anus and a continent sphincter. It also greatly simplified the problem of collecting specimens of feces.

During this series of experiments, three animals were used: dog 1, a fox terrier weighing 5.8 Kg. at the beginning of the experiment; dog 2, a mongrel, weighing 9.9 Kg., and dog 3, a mongrel, weighing 15.6 Kg. Largely perhaps on account of the daily experimenting with single foods, the animals tended to lose weight, but this tendency was counteracted by giving them plenty of food on Sundays and during occasional rest periods.

The animals were fed only once a day, about 8:30 a. m. One dog ate greedily anything that was given him, but the other two sometimes objected to certain foods and had to be fed either by tube or by dropping the material on the back of the tongue. Within from fifteen to thirty minutes after feeding, the animals were fastened comfortably either in the lateral recumbent or in the crouching position. Samples were collected at hourly intervals for eight hours, and the animals were then put into metabolism cages. In the morning any fecal material found on the floor of the cage or in the rectum, was examined microscopically; if it contained food remnants, it was added to the samples from the day before, but if it was a typical, dark, foul-smelling, amorphous "hunger stool," it was thrown away. Ordinarily, with foods that did not contain cellulose, there was little if any residue after the first eight hours.

The fecal material was collected with the help of a glass tube, 15 cm. in length and about 1 cm. in diameter to which petrolatum had been applied; this tube was passed through the anus. Any fluid present immediately flowed out, and solid feces were then forced into the tube by the straining of the animal. During the first few weeks, some stools were voided normally, but later the animals practically always waited until the tube was passed. Any fecal material adhering to the side of the tube was washed out with a measured amount of distilled water, and the whole specimen was then weighed. Note was made of the color, odor, consistency, reaction and microscopic appearance of the material, and the specimen was then dried to constant weight.

FASTING RESIDUES

When food was not given for twenty-four hours, only a small amount of dark brown material appeared. It had the consistency of thin mush and the odor was offensive like that of the usual dog's stool. Table 3 shows the amounts of moist and dry material excreted in twenty-four hours by each of the three dogs (chart 1). The reaction was always neutral to litmus paper. Microscopic examination showed granular material with occasional epithelial cells.

TABLE 3.—*Amounts of Moist and Dry Material Excreted During Twenty-Four Hours*

Dog	Weight, Kg.	Total Fecal Output in Grams in 24 Hours		Output of Moist Stool for Each Kilogram of Body Weight
		Moist	Dry	
1	6.8	9.16	2.17	1.35
2	9.9	15.37	2.47	1.16
3	15.6	18.09	3.09	1.55

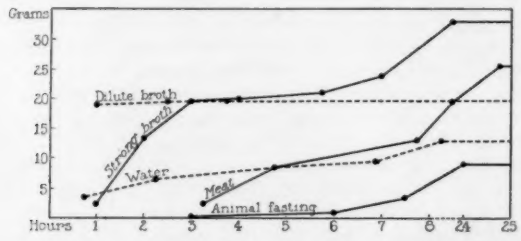

Chart 1.—The rate and quantity of excretion of moist residues (expressed in grams) for meat and broth; also the amount of fecal material obtained during fasting and after the giving of water.

CHARACTERISTICS OF FECAL MATERIAL WITH DIFFERENT DIETS

When the animals were fed with protein foods, meat, liver, gelatin and concentrated broth, the stools resembled closely those obtained from fasting animals. Only once was the reaction faintly alkaline, and that was when hashed meat was used. When the animals were fed on gelatin, the stools were light colored and had little odor; when meat was used, they were dark and usually fetid.

Food consisting mainly of carbohydrate, such as rice, bread, banana, apple and sugar gave rise to light canary, golden yellow or russet colored stools. They were mushy in consistency but somewhat thicker than the protein stools. They gave off little odor. Those obtained after feeding raw banana were fluid. After meals of dextrose, sucrose and lactose, the stools contained reducing substances.

When the animals were given lard, the stools were generally yellow, mushy and putrid; when they were given butter, the stools were watery and soapy. In one dog, who vomited some of the butter, neutral fat could be seen in the stool. The fatty stools did not seem to contain more bile than others.

RATE OF PASSAGE

Protein.—From 140 to 300 Gm. of lean meat or liver were fed, representing from 13 to 22 Gm. for each kilogram of body weight. Although the rate of passage varied even in the same animal on different days, it was usually slow; in some experiments, nothing appeared at the anus for four and a half hours. Gelatin and hard boiled egg went through the bowel slowly, like meat, but raw egg albumin went through rapidly (chart 2).

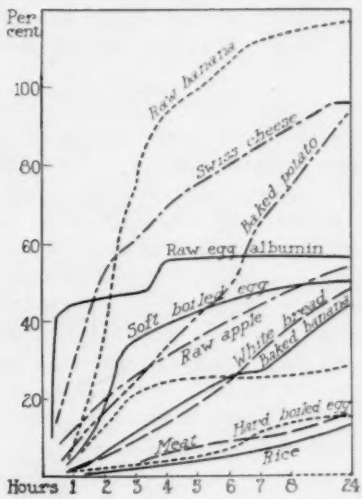

Chart 2.—Percentages of the amounts eaten, the rate and amount of excretion, of moist fecal residues from various foods. Most of the curves represent averages from several experiments.

Carbohydrate.—From 150 to 350 Gm. of boiled rice, farina, bread or baked potato were given at one time. This represented from 9.6 to 33.6 Gm. for each kilogram of body weight. The residues from rice appeared early, but, on the whole, they came through even more slowly than did those from meat. The residues from the other carbohydrate foods usually came through rapidly.

Fats.—Pure lard and butter were given in amounts of from 68 to 156 Gm. or about 10 Gm. for each kilogram of body weight. In

only one dog did this amount of butter cause nausea, and in this animal the material went through so rapidly that some of it was untouched by the digestive juices. Butter passed through the small intestine about as fast as some carbohydrates, but lard passed through at a rate intermediate between that of protein and carbohydrate. These experiments with protein, carbohydrate and fat give considerable support to Cannon's observations.

Fruits.—Canned pineapple, raw and baked apple with the skin removed, raw and baked banana, and purée of prunes were given in amounts of from 13 to 22 Gm. for each kilogram of body weight. The banana and pineapple were cut into small pieces, and the apple was passed through a meat chopper. The residues from the bananas, apples and prunes came through rapidly, in from one half to three fourths of an hour. The residue from the pineapple began to appear two and a half hours after the feeding, and it kept on appearing for twenty-eight hours or more. The food was little affected by the digestive juices.

Liquid Foods and Water.—Water given by stomach tube in amounts representing 36.7 cc. for each kilogram of body weight seemed to wash through a little more material into the terminal ileum, or perhaps it increased the amount of excretion into the bowel (chart 1). The amounts of feces obtained for each kilogram of body weight in the three dogs given water were 1.91, 1.37 and 2.38 Gm. Without water the figures were 1.35, 1.16 and 1.55 Gm. Strained broth, so concentrated that it would jelly, was given in amounts of 36.7 cc. for each kilogram. As may be seen from chart 1, it seemed to be stimulating to peristalsis, so that the residues came through more rapidly and in larger amounts than did those of its constituents, water and meat. Ordinary thin broth ran through the bowel even more rapidly; so Heile's experience with soups is confirmed.

Sugars.—When we gave 250 cc. (36.7 cc. for each kilogram) of a 4.2 per cent solution of lactose, corresponding to the concentration found in milk, the first residues appeared within fifteen minutes, and the rate of progress through the bowel was so rapid that nothing could be obtained after four and a fourth hours. This result so closely duplicated those of Strashesko that no further experimenting was done with lactose. The giving of 343 cc. of a 33 per cent solution of dextrose caused material to appear at the anus within thirty minutes. Progress was not so rapid as with lactose, but the bowel was empty after four and a half hours. In another experiment, 343 cc. of a 33 per cent watery solution of "karo" was given; material appeared in thirty minutes, but progress was slower than with pure dextrose, and most of the residue was obtained between the fourth and sixth

hours. After that the excretion stopped. Excretion was rapid also if the animal was given 109 cc. of a 50 per cent solution of sucrose, but residues kept coming away for seven hours.

Milk.—Whole milk was given in amounts of 36.7 cc. for each kilogram. The first specimen appeared in thirty minutes, and at the end of three hours most of the residues had passed. No constant difference could be observed in the behavior of raw and boiled milk, which is of interest in view of the widespread belief that boiled milk

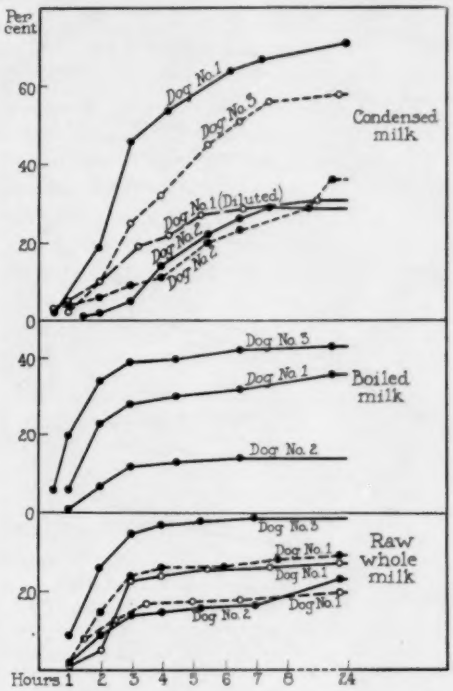

Chart 3.—Percentages of the amounts eaten and the rate and amount of excretion of moist residues from fresh, boiled and condensed milk.

is particularly efficacious in the treatment of diarrhea. An interesting peculiarity about the excretion of milk residues, well illustrated in chart 3, is the marked divergence in the results obtained with the three dogs; the shape of the curves is the same in each instance, but dog 2 always digested the milk better than did dogs 1 and 3. This marked difference in the resorptive powers of the animals was more constant and striking with milk than with any other food. As will be seen from chart 4, it was much less apparent when milk was added to

other foods, such as farina, but even then the digestive powers of the dogs fell into the same sequence. Heile noticed that some of his dogs did not digest food as well at some times as they did at others, and he thought the difference was due to the presence of enteritis, but this can hardly be the explanation for the differences obtained in our experiments. Condensed milk (Carnation brand) was given, either undiluted or diluted with equal parts of water, in amounts of from 21.7 to 44 cc. for each kilogram of body weight. The residues came through more slowly at first, so that the curves of excretion are different from those

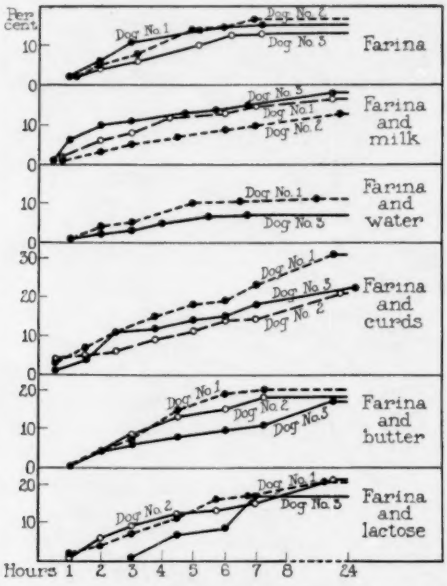

Chart 4.—Percentages of the amounts eaten, and the rate and amount of excretion of moist residues from farina, from farina and milk and from some of the constituents of milk.

obtained with fresh milk. The condensed milk was not digested as well as was the fresh milk.

Swiss cheese was given grated in amounts of 26.4 Gm. for each kilogram. The rate of progress was rapid, and within thirty minutes enormous amounts of fluid residue were obtained (chart 2). Even after five and a half hours, the fecal output was still large. Cottage cheese (grade A, apparently full of fat) was given in amounts of from 22 to 29.4 Gm. for each kilogram. The time of appearance of the residues was variable, in one experiment being as late as the fifth hour, and the curve of excretion was flat like that of meat.

INFLUENCE OF MILK AND MILK CONSTITUENTS ON THE DIGESTION OF OTHER FOODS

In view of the decided statements made by Berlatzki and others with regard to milk, it seemed advisable to check their results with care. A number of experiments were carried out first to establish the normal rate of passage for cooked farina. With 22 Gm. for each kilogram of body weight the residues appeared early, as one would expect with a carbohydrate food. When an equal amount of whole milk was added, there was little change in the rate of progress; in one experiment it was considerably accelerated, but in another it was a little slower than usual. Chart 4 shows the results with the three dogs. In order to determine whether more pronounced effects could be obtained with any constituent of the milk, the dogs were given, besides farina, amounts of water, butter, curd and lactose equal to those contained in the milk given in the previous experiments. It was found that water somewhat increased the rate of progress of food, while butter and lactose had no constant effect; lactose increased the total amount excreted. When crude casein (made by adding junket to milk, expressing the whey through cloth for twenty-four hours, and washing for a short time in water) was added to the farina, the rate of progress was slightly accelerated, and the total amount of moist residue was considerably increased. The addition of milk to bread regularly decreased the percentage of moist residue as did the addition of broth to bread.

From this work it appears that, at least in the dog, the addition of milk to other foods does not interfere with digestion as much as Berlatzki thought; what interference there is seems to be due to casein or lactose. More work is needed to show why casein in the form of cottage cheese was well digested, while in the form of junket or Swiss cheese it was poorly digested.

THE AMOUNT OF RESIDUE WITH DIFFERENT FOODS

Table 4 shows the percentage of moist and dry residues obtained after the giving of various foods. These foods have been arranged so far as possible in the order of their digestibility, as judged by the percentage of moist residue appearing at the anus. Among those with the least residue are gelatin, sucrose, dextrose, "karo," concentrated broth, hard boiled egg, meat, liver, rice, farina and cottage cheese; among those with the largest residues are fruits, potatoes, bread, lard, butter, Swiss cheese, soft boiled egg, raw egg albumin, milk and lactose.

The lowest dry residues were seen with dextrose, sucrose, gelatin, liver, meat, bread and milk, lard and butter. The largest dry residue was 85.9 per cent, seen with raw egg albumin. Other high dry residues, approximately 57 per cent, were seen with potato, raw banana, lactose, raw apple and broth.

TABLE 4.—*Percentage of Moist and Dry Residues Obtained with Various Foods*

Dog	Food	Forced Feeding	Total Amount of Food, Gm.		Per Kilogram	Total Residue, Gm.		Percentage of Residue		Percentage of Water
			Moist	Dry		Moist	Dry	Moist	Dry	
2	Gelatin	Yes	364.3	71.2	36.7	17.22	2.39	4.7	3.4	86.1
1	Dilute broth	No	246.8	2.9	36.7	19.70	1.19	7.9	41.0	93.9
2	Dilute broth	No	360.0	4.2	36.7	35.88	1.79	9.9	42.3	95.0
3	Dilute broth	Yes	567.1	6.7	36.7	59.57	2.02	10.5	30.3	90.6
3	Dextrose, 33 per cent	Yes	507.7	171.6	22.0	53.53	2.83	10.5	1.7	94.7
3	"Karo," 33 per cent	Yes	507.7	134.2	24.9	55.70	7.14	10.6	5.3	87.2
2	Sucrose, 50 per cent	No	215.5	108.9	11.0	23.79	3.52	11.0	3.2	85.2
3	Farina, water	Yes	678.9	56.8	43.5	44.83	5.82	6.6	10.2	87.0
1	Farina, water	Yes	296.9	24.9	43.7	32.76	4.46	11.0	17.9	86.4
3	Strong broth	No	569.2	28.4	36.7	56.96	7.64	10.0	26.9	86.6
1	Strong broth	No	249.6	12.5	36.7	32.80	5.29	13.1	42.5	82.9
2	Strong broth	No	369.5	18.4	36.7	51.45	6.66	13.9	36.1	87.1
1	Rice	Yes	229.6	48.9	33.8	26.02	4.92	11.6	10.1	81.5
1	Rice	Yes	219.6	45.3	32.3	29.85	4.68	13.6	10.3	84.3
1	Rice	Yes	174.8	40.2	25.6	23.75	4.60	13.6	11.5	80.6
2	Liver, hashed	No	200.0	75.0	20.2	20.54	3.83	10.3	5.1	81.3
3	Liver, hashed	No	200.0	75.0	12.8	31.94	4.23	16.0	5.6	86.7
1	Liver, hashed	No	150.0	56.3	22.0	26.02	4.10	17.3	7.3	84.2
2	Liver, lumps	No	200.0	75.0	20.2	25.31	4.77	12.7	6.4	81.1
3	Liver, lumps	No	200.0	75.0	12.8	25.65	3.89	12.8	5.2	84.8
1	Liver, lumps	No	150.0	56.3	22.0	23.39	4.67	15.6	8.3	80.1
1	Meat, lumps	No	150.0	42.9	22.0	17.69	3.38	11.8	7.9	80.9
1	Meat, lumps	No	300.0	85.8	44.0	41.32	6.74	13.8	7.9	83.7
1	Meat, hashed	No	140.0	40.0	20.6	21.30	3.87	15.2	9.6	81.8
1	Meat, hashed	No	150.0	42.9	22.0	24.93	5.39	16.6	12.5	78.4
1	Meat, hashed	No	150.0	42.9	22.0	25.52	4.62	17.0	10.8	81.9
1	Cottage cheese	No	150.0	37.4	22.0	21.75	3.50	14.5	9.4	83.9
1	Cottage cheese	No	200.0	49.8	29.4	31.29	5.10	15.6	10.2	83.7
1	Egg, hard boiled	No	246.5	64.8	36.2	37.21	6.33	15.1	9.8	82.9
1	Farina, broth	No	179.8	25.9	26.4	21.34	2.43	11.8	9.4	88.6
1	Farina, broth	No	179.8	25.9	26.4	27.19	3.23	15.1	12.4	88.1
3	Farina	Yes	343.0	56.8	22.0	42.96	5.02	12.5	8.8	88.3
1	Farina	Yes	150.0	24.9	22.0	22.45	2.72	15.0	10.9	87.9
2	Farina	No	218.0	36.1	22.0	37.96	4.83	17.4	13.3	87.2
2	Farina, butter	No	225.1	42.7	22.7	40.08	4.75	17.8	11.1	88.1
3	Farina, butter	No	354.5	67.1	22.7	60.34	8.96	17.0	13.3	85.2
1	Farina, butter	No	155.0	29.4	22.8	30.94	3.39	19.9	11.5	89.0
2	Farina, milk	No	441.0	63.4	44.5	58.35	9.28	13.2	14.6	84.1
1	Farina, milk	No	303.4	43.6	44.6	50.71	6.86	16.7	15.7	86.5
3	Farina, milk	No	693.9	99.7	44.5	128.04	16.88	18.4	16.9	86.8
3	Farina, lactose	Yes	357.5	72.4	23.0	59.01	7.87	16.5	11.0	86.6
1	Farina, lactose	Yes	156.4	31.2	23.0	32.37	5.68	20.7	18.2	82.5
2	Farina, lactose	No	227.2	45.4	23.0	48.70	7.42	21.4	16.4	84.8
2	Farina, casein	No	206.7	54.8	26.9	55.59	8.33	20.8	15.2	85.0
3	Farina, casein	Yes	425.5	88.4	27.3	92.08	11.45	21.6	13.0	87.6
1	Farina, casein	No	189.2	39.9	27.8	58.16	6.83	30.7	17.1	88.3
1	Milk	No	255.7	31.3	36.7	50.46	4.83	19.7	15.4	90.4
2	Milk	No	373.3	45.6	36.7	85.45	9.95	22.9	21.8	88.3
1	Milk	No	255.7	31.3	36.7	68.66	8.23	26.8	26.3	88.0
1	Milk	No	255.7	31.3	36.7	75.21	7.67	29.4	24.5	89.8
3	Milk	No	588.1	71.9	36.7	227.50	21.54	38.7	29.9	90.1
1	Lactose, 4.2 per cent	Yes	255.4	10.6	36.7	66.79	6.02	22.2	56.8	91.0
3	Bread, milk	No	303.4	135.3	19.4	59.34	8.38	19.5	6.2	85.9
2	Bread, milk	No	303.4	135.3	30.6	60.91	10.68	20.1	7.9	82.5
2	Bread, milk	No	303.4	135.3	30.6	65.43	11.49	21.8	8.5	82.4
2	Bread, milk	Yes	303.4	135.3	30.6	68.50	12.44	22.2	9.2	81.8
3	Bread, milk	No	303.4	135.3	19.4	91.77	13.59	30.0	14.8	88.4
1	Bread, milk	Yes	303.4	135.3	44.6	92.54	13.59	30.5	10.0	85.3
2	Bread, broth	Yes	298.8	121.9	30.2	60.79	10.95	20.4	8.9	81.9
1	Bread, broth	Yes	298.8	121.9	43.9	76.21	11.60	25.5	9.5	84.8
3	Bread, broth	No	298.8	121.9	19.2	79.75	11.81	26.8	9.6	85.2
1	Condensed milk diluted	No	308.7	39.5	44.0	94.80	11.18	31.2	28.3	88.0
2	Milk, boiled	No	352.9	47.5	36.7	50.44	6.76	14.3	14.1	86.6
1	Milk, boiled	No	252.1	33.9	36.7	89.64	10.65	35.6	31.4	88.1
3	Milk, boiled	No	514.2	69.2	36.7	221.52	21.19	43.1	30.6	90.4
3	Bread	Yes	150.0	116.5	9.6	66.96	12.16	44.6	10.4	81.8
1	Bread	Yes	150.0	116.5	22.0	70.82	10.89	47.2	9.3	84.6
2	Bread	No	150.0	116.5	15.2	79.08	13.29	52.7	11.4	83.2
2	Condensed milk	No	224.8	56.5	21.7	64.87	9.28	28.8	16.4	85.7
2	Condensed milk	No	224.8	56.5	21.7	80.22	10.98	35.7	19.4	86.3
3	Condensed milk	No	355.5	89.4	21.7	204.93	23.84	57.6	26.6	88.3
1	Condensed milk	No	156.7	39.5	22.0	111.37	12.05	70.9	32.1	88.6
1	Pineapple, canned	Yes	150.0	37.3	22.0	69.88	9.11	46.6	24.4	86.9
1	Egg, soft boiled	No	121.0	30.1	17.8	61.60	9.08	50.4	30.2	90.3
2	Lard	No	99.0	99.0	10.0	43.21	7.25	43.6	7.3	83.2
3	Lard	No	156.0	156.0	10.0	72.02	11.91	46.2	7.6	83.5
1	Lard	No	68.0	68.0	10.0	39.33	6.32	57.8	9.3	83.9
1	Raw egg albumin	Yes	178.5	21.3	26.2	100.92	18.34	56.5	85.9	81.8
3	Banana, baked	Yes	340.0	86.8	22.0	106.51	12.64	31.3	14.6	88.1

TABLE 4.—*Percentage of Moist and Dry Residues Obtained with Various Foods—(Continued)*

Dog	Food	Forced Feeding	Total Amount of Food, Gm. Moist	Total Amount of Food, Gm. Dry	Per Kilogram	Total Residue, Gm. Moist	Total Residue, Gm. Dry	Percentage of Residue Moist	Percentage of Residue Dry	Percentage of Water
2	Banana, baked	Yes	215.0	54.9	22.0	86.15	12.41	40.0	22.6	85.6
1	Banana, baked	Yes	150.0	38.3	22.0	87.76	11.40	58.5	29.8	87.1
3	Apple, baked	No	300.0	55.3	19.2	136.08	12.80	45.4	23.1	90.8
2	Apple, baked	No	200.0	36.8	20.2	101.01	10.80	50.5	29.5	89.2
1	Apple, baked	No	100.0	18.4	14.7	54.01	6.64	54.0	36.0	87.7
3	Apple, raw	No	300.0	38.1	19.2	147.10	17.45	49.0	45.8	88.1
1	Apple, raw	No	100.0	12.7	14.7	50.50	6.42	50.4	50.6	87.3
2	Apple, raw	No	200.0	25.4	20.2	118.36	9.67	59.2	38.0	91.8
3	Butter	No	156.0	140.4	10.0	96.90	11.15	61.5	7.9	86.3
2	Butter	No	99.0	89.1	10.0	72.98	11.35	73.7	12.7	84.4
3	Prunes, puréed	No	200.0	75.0	12.8	120.45	14.21	60.2	18.9	88.2
2	Prunes, puréed	No	200.0	75.0	20.2	154.65	18.68	77.3	24.9	87.9
3	Prunes, puréed	No	343.0	128.6	22.0	297.85	34.82	86.8	27.1	88.3
1	Prunes, puréed	No	87.0	32.6	12.8	79.35	10.44	91.2	31.9	80.8
2	Prunes, puréed	No	217.8	81.7	22.0	199.20	24.33	91.5	29.7	82.8
1	Prunes, puréed	No	150.0	56.3	22.0	159.36	17.16	106.2	30.5	89.2
1	Swiss cheese	Yes	179.8	116.8	26.4	171.79	12.87	95.6	11.0	92.5
2	Potato, baked	No	217.0	51.5	22.0	187.85	24.10	86.6	46.8	87.2
1	Potato, baked	Yes	150.0	35.6	22.0	140.79	15.76	93.8	44.3	88.8
3	Potato, baked	No	343.0	81.3	22.0	348.58	46.91	101.6	57.7	86.5
2	Banana, raw	Yes	215.0	44.9	22.0	211.89	17.48	98.5	38.9	91.7
1	Banana, raw	Yes	150.0	31.4	22.0	167.96	10.25	111.97	32.7	93.8
3	Banana, raw	Yes	340.0	71.1	22.0	481.01	40.31	141.4	56.7	91.6

Raw egg albumin is dietetically a most interesting substance. It is well known that it runs through the stomach and out of the pylorus undigested, and we found that it goes through the small bowel in the same way; in fact, in these experiments it was seen to run out of the rectum unchanged. Similar observations have been made by Bateman, who found that when he gave considerable amounts of raw white of egg to dogs, rats, rabbits and man, it caused diarrhea. It appeared to be utilized to the extent of from 50 to 70 per cent only. Even in animals with an intact colon, the feces were liquid, soft, or pasty, and contained unchanged egg-white. In a small dog, two raw eggs produced softening of the feces, while four or five produced diarrhea. They had this effect even when mixed with other foods. Dried egg-white was found to be just as indigestible as the liquid substance.

The work of Aufrecht and Simon [10] suggests that raw egg is much better tolerated by man than by the dog, but their results are so divergent from ours and those of Bateman [11] that the subject should be further investigated. Chart 2 shows the striking differences in the digestibility of raw, soft boiled and hard boiled eggs.

The high percentage of dry residue obtained after giving lactose is of interest because this substance is supposed to be almost unabsorbable by

10. Aufrecht, S., and Simon, F.: Ueber Nährwert und Ausnutzung roher und weichgekochter Hühnereier, Deutsche med. Wchnschr. **2**:2308, 1908.

11. Bateman, W. G.: The Digestibility and Utilization of Egg Proteins, J. Biol. Chem. **26**:263, 1916.

the mucous membrane of the bowel. For this reason, it may increase the fluidity of the intestinal contents and act as a laxative in much the same way as does magnesium sulphate.

The highest percentage of moist residue was found with raw banana (141.4 and 111.97 per cent), and this food sometimes gave rise to stools larger than the original meal. Other foods giving stools slightly larger than the meal were prunes (106.2 per cent) and baked potato (101.6 per cent). Large moist residues were obtained also after feeding lard, butter, Swiss cheese, apple, milk, raw egg albumin and bread.

The large stools obtained with prunes and baked apple were to be expected in view of the well known laxative properties of these foods. Our experiments suggest that bananas also might be used in the treatment of patients who are constipated. Von Noorden and Salomon [12] call attention to the fact that in Germany potatoes are sometimes used for this purpose; when eaten in large quantities, they give rise to large mushy stools. It is well known also that butter and cream are slightly laxative when given in sufficient amounts.

The large residue obtained with milk is interesting because it throws light on the fact that this food is not well tolerated by many persons. After taking considerable quantities of it, many become constipated, others are troubled with diarrhea, and in both groups there are many who suffer from flatulence and "biliousness." The poor digestibility of cow's milk has been commented on by Voit, Prausnitz and many other authorities quoted by von Noorden and Salomon. The last named writers comment on the fact that milk is not so well utilized in the bowel as are eggs, meats or even some of the softer vegetables. They estimate, from experiments reported by many workers, that when milk is ingested the percentage of dry substance excreted in the stools of healthy men and women is about 7.1 per cent.

Influence of Comminution.—Strange to say, when meat or liver was given in the form of lumps, the percentage excreted was a little smaller than when the food was given hashed. It must be remembered, however, that the dog's digestive tract must be particularly well prepared for the handling of unchewed food.

Influence of the Amount of Food Given.—One would expect the amount of moist residue to vary directly with the amount of food given, and we found this to be true. One would expect also that when the amount given exceeds that which the intestine can handle efficiently, the percentage excreted would rise rapidly. Müller noticed that in normal

12. Von Noorden, K. H., and Salomon, Hugo: Handbuch der Ernährungslehre, Berlin, Julius Springer, 1920, p. 1.

dogs fed with fatty foods a certain amount could be handled satisfactorily, but when this was exceeded, the stools immediately became voluminous, foul and full of neutral oil. He apparently was unable to reach the upper limit of tolerance for meat, because, even when he gave 2,500 Gm. to a dog weighing 35 Kg., digestion was a little more complete than when he gave 500 Gm. So far as our experiments went, they showed the same result; the meat was always well digested, but on some occasions we probably gave more fat than the animal could digest. More work might well have been done on this phase of the problem.

SUMMARY

The experiments here reported suggest that the best basis for a low residue diet is lean meat. To this might be added rice, hard boiled eggs, sugars (except lactose) and probably small amounts of fruit juices, tea and coffee. The highest degrees of absorption could probably be secured by giving small amounts of food several times during the day. Our experience with the dogs, together with that of Beuttenmüller [13] with a patient with a fistula in the terminal ileum, suggests that less material will be carried into the colon if the diet is kept fairly dry.

There is considerable evidence both in the experiments here reported and in the literature to show that when it is desired to prevent bowel movements, milk should not be given. The large residue often left in the terminal ileum after the taking of milk may account for the fact that it is not well tolerated by many persons and that it makes them "bilious." This is a point that we think should be brought to the attention of the medical profession, because there is a tendency on the part of many physicians to prescribe milk and sometimes nothing but milk whenever they wish to give the digestive tract a rest. They are prone to prescribe it also in cases of diarrhea, although it appears that it is one of the first foods they should interdict. It has been our experience that milk has a bad effect on many persons with diarrhea who promptly get well when given nothing but meat or meat with a little pure starch and sugar.

It is interesting to see how closely our figures for percentage of fecal residue with different foods agree with many of those obtained on animals and man with the colon intact. It supports other observations showing that the mucous membrane of the colon absorbs little besides water.

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13. Beuttenmüller, Helene: Beobachtungen an einer Zoekalfistel, München. med. Wchnschr. **1**:743, 1920.

Attention is called again to the peculiar indigestibility of raw egg albumin, an important point because some physicians and most laymen believe that there is nothing more nourishing than a raw egg.

Curious also was the inability of the dogs to digest raw banana, Swiss cheese, baked potato and white bread. We were not surprised at their inability to digest apple, because this fruit is not tolerated by many men and women.

STREPTOTHRIX NECROTIC BRONCHOPNEUMONIA *

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The clinical similarity of mytotic infection of the lung to tuberculosis renders the differential diagnosis of both therapeutic and prognostic importance. Since but relatively few cases of infection by *streptothrix*, as distinguished from actinomycosis, have been recognized and reported, the following record of a case seems pertinent.

REVIEW OF THE LITERATURE

Cohn [1] in 1875 first gave the name *Streptothrix foersteri* to a filamentous branched organism isolated from a lacrimal duct concretion.[1a] Eppinger,[2] however, gave the first classic description of a case—an abscess of the brain from which a pure culture could be isolated using the ordinary mediums. He named this fungus *Cladothrix asteroides*. Further work confused this organism with the organism now known, at least generically, as *Actinomyces* (Bollinger [3]), which is especially characterized by the sulphur granules, clubbed ends of the filamentous mycelium and the fact that it is most commonly seen in the "lumpy jaw" infections of cattle.

In 1888, Nocard [4] described an organism which was later termed *Streptothrix farcinica*, isolated from a disease indigenous in the Guadeloupe Islands and known as "farcin du boeuf." De Toni and Trevisan [5] named the whole group *Nocardia* in honor of the discoverer of *Streptothrix farcinica*.

The name *Cladothrix asteroides* was changed by Rossi Doria [6] in 1891 to *Streptothrix eppingeri*, because the false branching of *Cladothix* was not present.

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2. Eppinger, H.: Ueber eine neue, pathogene Cladothrix, Beitr. z. path. Anat. u. z. allg. Pathol. **9**:287, 1891.

3. Bollinger, O.: Ueber eine neue Pilzkrankheit beim Rinde, Centralbl. f. d. med. Wissensch., 1877, p. 481; Deutsche Ztschr. f. Thiermed. **3**:334, 1877.

4. Nocard, E.: Note sur la maladie des boeufs de la Guadeloupe, Ann. de l'inst. Pasteur, 1888, vol 2, p. 293.

5. De Toni and Trevisan: Schizomycetaceae, Saccardo—Sylloge fungorum, 1889, vol. 8.

In 1898, von Lachner-Sandoval [7] reviewed the matter and attempted to settle it on the grounds of priority. The name *Nocardia* is antedated by both *Streptothrix* and *Actinomyces* and hence is rejected by him. The name *Streptothrix* was given by Corda [8] to a subdivision of *Hypomycetes,* and is still in use for those fungi. By exclusion, *Actinomyces* remains as the generic name.

Thus, MacCallum and his associates use this terminology. As Wright [9] has pointed out, however, the biologic characteristics of the organism isolated by Nocard are widely divergent from the characteristic *Actinomyces bovis* or "ray fungus." Therefore, he does not see any justification for the classification of such varied organisms as *Actinomyces bovis* and the variously named *Nocardia, Streptothrix,* etc., as described by Nocard and Eppinger under one heading. His belief is that usage renders the name *Streptothrix* justifiable. While this solution is certainly far from satisfactory, until more cases are carefully studied it seems best to use this classification. Hence the name *Streptothrix* is used in this paper to be synonymous with *Nocardia, Actinomyces asteroides, Streptothrix eppingeri* and *Cladothrix asteroides,* following Wright's studies, as distinct from the "ray fungus" or *Actinomyces bovis.*

That the literature of the subject is greatly confused should cause little wonder. It is the dénouement of an evanescent systematization.

In general, the organism shows true branching, and the ends are not clubbed; it is gram-positive. When treated with carbol fuchsin and then with Gabbett's decolorizing solution it retains the stain, and to some extent when treated with an acid alcohol (Czaplewski's reagent). It grows well on potato and agar aerobically. MacCallum,[10] Steele,[11] Henrici and Gardner,[12] and Musgrave, Klegg and Polk [13] give excellent descriptions of these characteristics. Wheal and Chown's staining method [14] is said by Gibson [15] to be useful for staining the mycelium in tissues. Feistmantel [16] first carefully studied the acid fast qualities of the organism.

6. Rossi, Doria: Ann. d. Inst. d'ig. sper. d. Univ. di Roma **1**:4, 1891.

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(Footnotes continued on following page)

Many authors have contended, probably justifiably, that there are many transitional forms among this group of organisms. It may well be that the organisms are allotropic, but until such changes in state can be correlated with environment, it would seem better to describe, without attempt to distort the picture by forcing a doubtful classification,

Clinically *Streptothrix* does not show the rather specific predilections shown by *Actinomyces*. *Streptothrix* exhibits the most diverse types of infection, that of the lung probably being the most common. Isolation and identification of the organism seems the only reliable diagnostic criterion.

As far as I have been able to determine the following authors have described cases of streptothricosis: Fränkel and Schottmüller,[17] Almquist,[18] Gasperini,[19] Sauvageau and Radais,[20] Sabrazis and Riviere,[21] Ferre and Faquet,[22] Scheele and Petruschky,[23] Buchholtz,[24] Ruge,[25] Rullmann,[26] Berstnew,[27] Maresch,[28] Flexner,[29] Chiari,[30] Norris and

15. Gibson, A. G.: On the Infective Nature of Certain Cases of Splenomegaly and Banti's Disease, Quart. J. Med. **7**:153, 1914.

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Larkin,[31] Aoyama and Miyamoto,[32] Birt and Leishman,[33] Trolldeiner,[34] Horst,[35] Engelhardt and Löhlein,[36] MacDonald,[37] Stokes,[38] Schbad,[39] Tuttle,[40] Butterfield,[41] Bridge,[42] Potron and Théry,[43] Steele and Lee,[44] Gibson,[45] Davis and Garcia,[45] Pijper,[46] Christopherson and Archibald,[47] Finch and Jessup,[48] Evans,[49] Guy,[50] Glaser and Hart,[51] Lenchartz,[52] Henrici and Gardner,[53] Iacono,[54] Callender,[55] Gougerot [56] and Levy.[57]

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(Footnotes continued on following page)

REPORT OF A CASE

History.—An Irish chauffeur, aged 41, complained of hemoptysis for eight months, without associated pain in the chest. During childhood, he had measles and whooping cough. Thirteen months before admission, the patient had a rather severe lobar pneumonia on the right side, and three months later a productive cough developed and persisted. A month later, he began suddenly to have a severe pain in the right side of the chest, associated with slight fever and a more violent cough. Within two or three days, the pain ceased, but the cough persisted. The patient then noticed streaks of blood in the sputum which had formerly been yellow. Four months later, a sudden severe hemorrhage occurred, with the loss of a pint or more of blood. It was believed at another hospital that he had an abscess of the lung. After a nine weeks' stay at the hospital, the patient had recovered sufficiently to return to work. One year after the onset of his trouble he had another severe hemorrhage which caused his admission to the New York Hospital. During his stay, a continuous hemoptysis was in progress. After two days in the hospital he had another severe hemorrhage during which he died.

Physical Examination.—The patient was well developed but showed a slight loss of weight (the average weight was 180 pounds [81.6 Kg.] and the present weight 160 pounds [72.6 Kg.]), rested comfortably, was slightly dyspneic and sweated profusely. The mucous membranes and nail beds were dusky and cyanotic.

The respiration was fast and shallow; expansion was about equal on both sides. The heart apex was in the fifth interspace, 11 cm. from the midline, the rate was 130 beats per minute and the action was regular without any abnormal sounds. The resonance was definitely impaired over the anterior lower two thirds of the right side of the chest. The breath sounds had a poor vesicular quality especially anteriorly over the right side of the chest. The voice sounds were unchanged. A few scattered râles were heard, especially in the right axilla. A friction rub was heard in the right posterior axillary line toward the lower lobe. Unfortunately, the chest could not be given a thorough examination, because of the almost continuous hemoptysis.

An indefinite superficial mass was felt in the upper left quadrant of the abdomen, with associated spasm and tenderness.

The nails were rather markedly clubbed. The examination otherwise did not reveal any thing pertinent.

The temperature was variable, with sharp drops and raises ranging from 100 to 105 F. The pulse rate closely paralleled the variations of the temperature. The respiration averaged 44 breaths per minute. The blood pressure was 115 systolic and 87 diastolic.

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Laboratory Examination.—The red blood cells numbered 4,880,000, the white blood cells numbered 11,200 (78 per cent neutrophils, 19 per cent lymphocytes, 3 per cent mononuclears) and the hemoglobin content was 70 per cent. The Wassermann reaction was negative. The urine showed a marked trace of albumin and sugar, and an occasional hyaline cast. The blood urea nitrogen was 17.4 mg. per hundred cubic centimeters.

The sputum was profuse, had a foul fecal odor and was blood stained and watery. Acid fast bacilli were not found on repeated examination. One clump of irregularly thickened, branching, gram-positive organisms were found.

Autopsy.—The heart weighed 330 Gm., but was of normal size and shape. On the anterior surface of the right ventricle, about 1 cm. from the tricuspid valve was a small cavity, 4 mm. in diameter, filled with greenish yellow purulent material. The endocardium, valves and coronary vessels were normal. A round mass similar to a thrombus was seen lying in the lumen of the right ventricle. The center of this mass was occupied by *Streptothrix*. The pericardial cavity contained a moderate amount of turbid serous fluid.

The right lung weighed 1,075 Gm. Scattered over the surface were numerous deep grayish-blue areas in which yellow patches were seen. These areas appeared to be consolidated. On section, the larger part of the cut surface was found to be occupied by grayish granular consolidated masses which in most instances showed central necrosis. At numerous places in these masses of consolidation were central cavities filled with greenish-black, foul smelling material. Other masses presented innumerable small yellowish-gray foci scattered through a reddish-gray consolidated matrix. These lesions were most advanced in the lower lobe. The upper part of the lower lobe contained a cavity about the size of a walnut; the inner surface was deep red, and at one place a medium sized vessel was eroded. This erosion may reasonably be assumed to represent the source of the hemoptysis. The cavity communicated with a bronchus. The mucosa of the bronchi was deeply injected and covered with a grayish-brown mucoid material. The left lung weighed 675 Gm. Lesions similar to those in the right lung but not so advanced were present throughout the left lung.

The peritoneal cavity did not contain an excess of fluid. Opposite the umbilicus and about 10 cm. to the left of the midline, the parietal peritoneum showed an indistinctly circumscribed, bluish-red discoloration. In the wall of this region a large abscess filled with thin brownish-gray material was found. This purulent material extended into the neighboring muscles forming fistulous tracts extending from the costal margin to the inguinal ligament.

The liver weighed 2,425 Gm.; it was normal in shape. On section, the normal markings were distinct. There was some passive congestion. The biliary system was apparently normal.

The spleen weighed 250 Gm., was very soft and the normal markings on section were found to be obscure. The larger part of the cut surface was of a pale pink color alternating with deep red areas, apparently the seat of large hemorrhages.

The gastro-intestinal tract and the pancreas were normal.

The left kidney weighd 250 Gm.; the right, 200 Gm. Nothing of importance was found in the examination of the kidneys. The pelvis and ureters did not show any gross lesions. The bladder and genitals were normal.

The aorta showed moderate sclerosis.

Histologic Examination.—The abscess showed the central grayish-blue granular masses of *Streptothrix*, surrounded by a zone of marked infiltration with poly-

morphonuclear leukocytes and plasma cells and rather extensive necrosis of the myocardium surrounding the cavity. Some of the muscle cells were filled with fat. This abscess is shown in figure 1.

Histologically, the yellowish-gray foci were found to represent abscesses in the lungs, showing a central, finely granular, grayish-blue mass, surrounded by a diffuse plasma and invasion by polymorphonuclear leukocytes. The walls of the blood vessels were often involved in the cellular exudation thus leading one to suspect that they might have been involved in the genesis of infected thrombi.

Fig. 1.—Abscess of the mycardium caused by *Streptothrix*, which is seen as dense matted material in the center surrounded and infiltrated with polymorphonuclear leukocytes and plasma cells.

The bluish granular mass was gram-positive and was identified by culture as *Streptothrix*. At numerous places small bronchioles were found to contain a marked cellular exudate with the central bluish granular mass of *Streptothrix*. One vessel contained a mural thrombus. In large areas the alveoli were filled with blood and in some places the resulting picture was that of hemorrhagic infarction. In certain portions the alveoli were filled with a homogenous pink staining material. Areas of consolidation with exudation of polymorphonuclear leukocytes and fibrin were present. The red and white blood cells were for the most part well preserved. Figure 2 shows one of the areas invaded by *Streptothrix*.

Except for the abscess in the abdominal wall, which was almost identical in structure with those described in the myocardium, the histologic examination did not reveal more of importance.

Bacteriology.—The organism was isolated on 2 per cent glucose agar. Branching hyphae with tapering ends were seen in such cultures. The organism was partially acid-fast and was gram-positive. Unfortunately, injections into animals were not made. The classification and isolation were carried out by Dr. Wheeler. Figure 3 shows the gram-stained *Streptothrix* in the myocardium.

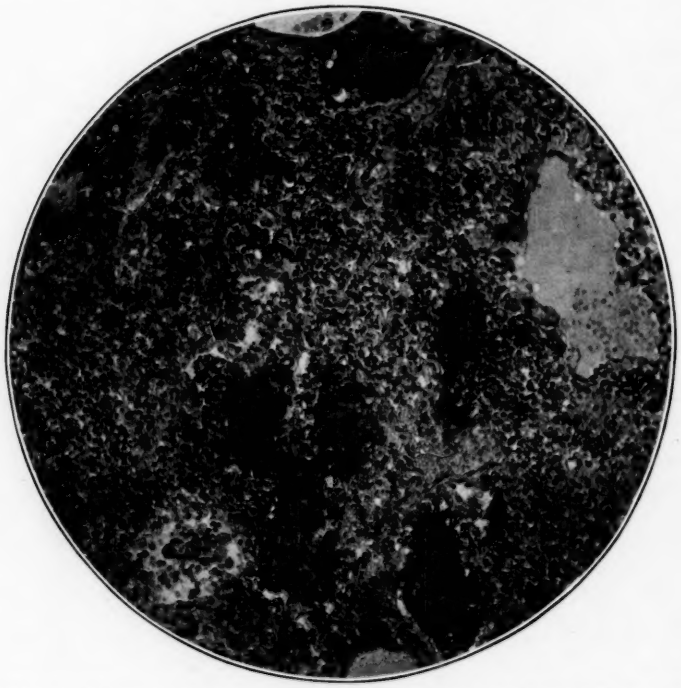

Fig. 2.—Abscess of the lung caused by *Streptothrix*. The dense, deeply stained material is *Streptothrix*.

COMMENT

Though streptothricosis closely simulated tuberculosis clinically, there was little in the gross or microscopic changes to cause confusion. As in most cases of this disease nothing was ascertained concerning the manner in which the infection was obtained. Clinically one was impressed in this case with the relatively acute course, associated with an almost continuous hemoptytis. Pathologically the condition was both aggressive and progressive, and it was characterized by the production of mycotic abscesses, from which arose metastases. These abscesses appeared to be invasive locally by direct extension.

Streptothrix asserts itself in the most protean form and the most varied locations—at times in the brain, at times in the lung and again in the peritoneal cavity. Hence, the symptoms depend on the location of the infection. In general, however, they consist of suppuration and inflammation. The localized formation of an abscess is the rule. Metastatic abscesses often occur in diverse parts of the body—the myo-

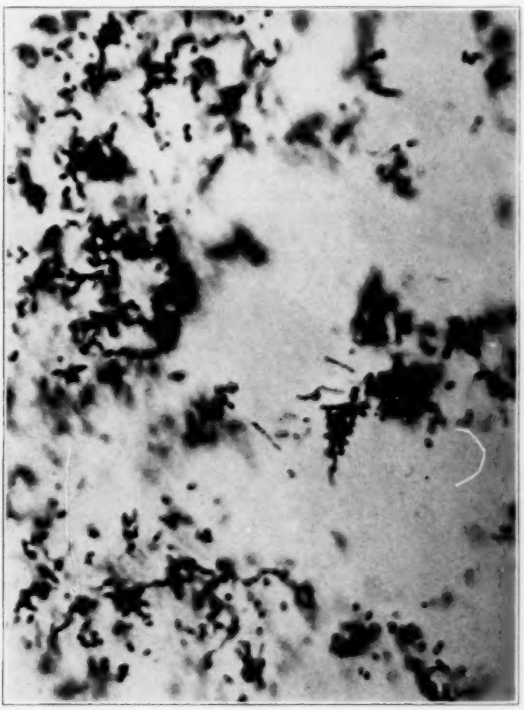

Fig. 3.—Gram stain of *Streptothrix*, as seen in the myocardium; × 1680.

cardium, the abdomen and the walls of the chest are common sites. The infection seems to be subacute or acute more often than chronic. The pulmonary cases usually simulate tuberculosis or pneumonia with either abscess or empyema. In the brain, the symptoms and signs are those of tumor or abscess.

The conditions from which *Streptothrix* infection must be commonly differentiated are: tuberculosis, pneumonia meningitis, actinomycosis, gumma and glanders. The only reasonably certain method of differentiation is the isolation and culture of *Streptothrix*, and its classification as to morphology, cultural characters and staining reactions, and usually its pathogenicity in guinea-pigs or rabbits.

Streptothrix infections offer difficulties for both the patient and the physician. The prognosis seems to be grave in the majority of cases.

Treatment with potassium iodide and autogenous vaccines has been tried with little success. The treatment so far is symptomatic, with the application of such surgical and medical procedures as are indicated by the location and the extent of the disease.

Book Reviews

INNERE SEKRETION. IHRE PHYSIOLOGIE, PATHOLOGIE UND KLINIK. VON DR. JULIUS BAUER. Price, 39 marks. Pp. 479, with index and 56 illustrations. Berlin: Julius Springer, 1927.

Dr. Bauer intended this monograph on endocrinology to be different from the usual monographs, and he has in part succeeded. In the preface he admits the present plethora of monographs on internal secretion, but despite their number, easy reference is still made to endocrine causes of almost all unknown or unexplained clinical symptoms and, as Dr. Bauer remarks, when disease of one endocrine organ does not seem sufficient to explain the phenomenon, the pluriglandular explanation, or direct disturbances due to lack of balance between the different endocrine glands is employed.

The author's point of view is made clear by the following quotation from the preface: "If we are to arrive at a true understanding not only of the interrelations of the endocrine organs but of the relation of the endocrine organs to normal and pathological processes, we must study these organs, not alone from the point of view of experimental physiology and pathological anatomy, but also from the point of view of more general biological correlations. We must consider their relation to the individual personality, to the individual constitution and to the geno-type. Many disturbances of the internal secretion are not, as most investigators seem to assume today, the cause of pathological processes which we observe in patients, but they are themselves consequences of wider disturbances of a general type, that is, disturbances that may be called primary anomalies of the constitution. Without thorough understanding of 'constitution-pathologie,' and the facts and theories of heredity real understanding of endocrinology is impossible." This point of view is maintained throughout the monograph and particularly in the last chapter which is entitled "The Relation of Internal Secretion to the Pathology of the Organism as a Whole as well as to the Pathology of Special Organs," and in the final supplement entitled "The Relation of the Internal Secretions to the Constitutional Habitus of Man."

The monograph is to be regarded as a serious contribution to medical science. There is undoubtedly an important element of truth in the author's point of view, but at present one may question whether the introduction of such concepts as geno-type, personality and heredity without further analysis of the mechanisms of these processes does not contribute more fog than clarity to an already difficult field. The author shows familiarity both with the experimental and clinical literature, and, in most cases, good critical judgment in the evaluation of this literature. For example, he says (page 183) "Organotherapy by mouth has so far proved successful only in the case of the thyroid gland." All experimentalists and critical practitioners will agree to that statement. One is therefore greatly disappointed on turning a few pages to find that the author apparently accepts as proved the idea that the activity of such glands as the ovaries, testes and hypophysis can be increased by diathermy; that with increased protein in the diet the secretion of the thyroid can be increased; that by the nonspecific protein therapy the activity of a number of the endocrine glands can be increased; that by sexual intercourse the hypoplastic ovaries in women can be improved; and that by the roentgen ray the activity of the ovaries and the hypophysis can be increased. All of these claims have been made on the basis of experimental or clinical observations; they have also been contradicted by equally good men; none of these claims are proved, and some of them are almost disproved.

The author gives abundant references to the literature in all the chapters, but, curiously, in a short list of larger works on the endocrines at the end

of the work, the author cites thirty German publications, but only two Italian, one English, one French and two American workers. This may be all right in a book intended primarily for German biologists and clinicians, but it does not give a fair impression of the available and valuable monographs in the different languages. On page 184, the author says: "Up till the present it has not been possible to control or prevent the symptoms that follow impairment of the hypophysis, the ovaries, the testes or the adrenals through any method of organotherapy." This statement has to be corrected in the case of the anterior lobe of the hypophysis for Smith and Evans have recently shown that daily parenteral administration of fresh anterior lobe of the hypophysis is able to overcome the symptoms of removing of the anterior lobe.

The present monograph will take its place with the best and the most suggestive, if not the most critical and conclusive in the field, in so far as it is possible for one man to write a standard work on this subject today.

AVITAMINOSEN UND VERWANDTE KRANKHEITSZUSTÄNDE. Herausgegeben von W. STEPP and P. GYÖRGY. Pp. 817, with index, and 194 illustrations. Berlin: Julius Springer, 1927.

This extensive monograph is the joint work of nine authors, the greater part of the work, however, being contributed by Dr. Stepp and Breslau and Dr. György of Heidelberg. In the preface the editors remark that previous monographs on diseases resulting from vitamin deficiency have been written mainly by laboratory men and thus give primarily the points of view of the experimental physiologists and pathologists. The present volume is intended to supplement previous efforts in that the material is presented and discussed essentially by clinicians, and mainly on the basis of clinical material. Nevertheless, the first 200 pages of the book deals primarily with experimental avitaminosis. These 200 pages are contributed by Dr. Stepp of Breslau, who writes on the physiologic side, and Dr. Kihn of Erlangen, who discusses the pathologic anatomy of avitaminosis. The chapters by Dr. Stepp are on the whole excellent summaries. The same cannot be said of the chapters by Dr. Kihn on the pathologic anatomy of experimental avitaminosis. As an example, the author's broad statement on page 162 regarding the pathologic anatomy of the alimentary canal in experimental avitaminosis—"The entire gastro-intestinal system shows the same changes, namely, extreme atrophy with tendency to necrosis of the mucosa." . . . "The intestinal rate is much decreased, the feces are held back, become concentrated and hard as stone." . . . "In all cases of experimental avitaminosis the alimentary tract becomes extremely atrophic." These are unwarranted and extreme statements. Such degree of pathology is not apparent, at least in the beginning of definite diseases resulting from vitamin deficiency in such animals as the dog, rat or pigeon.

Then follows a series of seven chapters by Dr. György of Heidelberg on Xerophthalmia, infantile tetany, osteomalacia, idiopathic tetany, scurvy, alimentary anemia in infants, and on the relation of vitamins to growth. These subjects are treated on the whole in an excellent and critical manner. Dr. György reaches the conclusion that infantile tetany is closely related to rickets and is primarily due to a deficiency of vitamin D rather than to any deficiency of the parathyroid glands. He reaches the same conclusion regarding the etiology of osteomalacia and idiopathic tetany in adults. There is a short chapter by Dr. Saile of Berlin on scurvy in adults; a short chapter by Dr. Nocht of Hamburg on the so-called ship beriberi, and short chapters on hunger edema by Dr. Shittenhelm of Kiel, and on scurvy by Dr. Fischer of Rostock. The rest of the book comprises excellent chapters on beriberi by Dr. Shimazono of Tokyo, and on pellagra by Dr. Lavinder of New York.

A monograph of this size and varied authorship necessarily contains errors both of omission and commission. For example, in the lengthy chapter on hunger edema by Shittenhelm (51 pages), the author leans toward the view that avitaminosis is the primary cause of the disease, and he seems not to be

familiar with the work of Dr. Kohman which shows that low protein in the diet is the essential cause of the malady. Nevertheless, the work must be regarded as a serious and, on the whole, successful effort to summarize our present knowledge of the diseases caused by vitamin deficiency for the aid and direction of the practicing physician. Every internist who is capable of handling German may pursue the monograph with profit.

INTRODUCTION TO THE STUDY OF EXPERIMENTAL MEDICINE. By CLAUDE BERNARD. (Translated under the auspices of the General Educational Board, by Henry Copley Green, A.M.), introduction by Laurence J. Henderson. New York: The MacMillan Company, 1927.

The translation of the book has rendered a real service to medicine by making it available to English readers. The subject is one in which Claude Bernard is deeply interested. His firm belief that the advancement of medicine was to be made in the laboratory is evident throughout. Time has shown the correctness of his prediction.

It is impossible in a review to give an adequate conception of the significance of the subject matter contained in this book. Perhaps a better insight may be acquired by making some quotations.

In his discussion of the difference and interrelation between observation and experiment, he accepts Cuvier's distinction. "The observer listens to nature, the experimenter questions and forces her to unveil herself."

"The art of investigation is the corner stone of all experimental science"

"In the experimental sciences all progress is measured by improvement in the means of investigation."

"Experiment is an observation induced with the object of bringing to birth an idea."

"We must observe without any preconceived idea; the observer's mind must be passive, that is, it must hold its peace; it listens to nature and writes at nature's dictation."

"The results of an experiment must be noted by a mind stripped of hypothesis and preconceived ideas."

"We must never make an experiment to confirm our ideas but simply to control them."

"Genius is revealed in a delicate feeling which correctly forsees the laws of natural phenomena, but this we must never forget, that correctness of feeling and fertility of idea can be established and proved only by experiment."

Dr. Henderson's introduction is in full accord with the spirit of the book. This volume can be read with profit by every active or prospective investigator in medicine.

THE NORMAL CHEST. By DR. J. A. MYERS. Price, $3.50. Baltimore: Williams & Wilkins Company, 1927.

This is, so far as I know, the first satisfactory book on the normal chest. Writers and teachers have usually avoided the subject for the excellent reason that it is almost impossible to interest students in it. In order to maintain interest one must write and teach about the normal and the abnormal chest in "their" contrasts with each other. That is just what this book does, and thereby it maintains interest. Some of the topics mentioned, despite the fact that they do not exist in the normal chest, are: plural and pericardial adhesions, anemia, aneurysm, angina pectoris, arhythmia, arteriosclerosis, hypertension, cavernous breathing, cardiac dilatation, convulsions, cyanosis, D'Espine's sign, ectopia cordis, emphysema, fibrillation, Flint's murmur, foreign bodies, friction sounds, exophthalmic goiter, heart block, heart murmurs, Hodgkin's disease, kidney disease, migraine, mitral stenosis, pectoriloquy pericardial effusion, pleurisy, pneumonia, pneumonothorax, râles (thirteen references), rickets, sarcoma, synocpe, syphilis, tuberculosis (nineteen references) and many others.

With this wholly sensible admixture of the diseases of the normal and the abnormal chest, one can make an interesting and helpful book, as Dr. Myers and his collaborators have done.

Among the most valuable chapters are those on the acoustics of auricular fibrillation and percussion, on the developmental anatomy of the chest and the roentgenogram of the normal chest.

Minor points with which I am not in agreement are the references to emphysema (a disease which has not, as yet, any known physical signs whereby it can be distinguished from the conditions existing in the "barrel chest" without emphysema) the remarks about "impure heart sounds" on page 148 and the sections on that useless survival, cardiac percussion.

But, as a whole, the book is excellent, and it may be confidently recommended to teachers and students of disease of the chest.

DISEASES OF THE DIGESTIVE ORGANS WITH SPECIAL REFERENCE TO THEIR DIAGNOSIS AND TREATMENT. By CHARLES D. AARON, Sc.D., M.D. Fourth edition, thoroughly revised. Price, $11. Pp. 927 with 174 engravings, 70 roentgenograms and 13 colored plates. Philadelphia: Lea & Febiger, 1927.

On the whole, the book is well outlined and complete. The chapters on laboratory tests and analyses are good. The author's statements concerning the indications for duodenal lavage (114 pages) and its therapeutic results, and intestinal toxemia (chapter XXXIX), however, are not generally accepted. The chapters on acute and chronic gastritis (XXII and XXIII) and gastroenteroptosis and the symptomatology attached thereto seem a bit overemphasized in the light of present knowledge.